

acta ophthalmologica

VOL. 54 FASC 1

A K. K. K. LUNDSGAARD EDI COEPTA

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The Eye Pathology Institute
and the Ophthalmological Tumour Centre
(Head S Ry Andersen)
University of Copenhagen Denmark

TUMOURS OF THE EYE AND ITS ADNEXA

BY

S RY ANDERSEN

A survey from the Eye Pathology Institute and the Ophthalmological Tumour Centre Copenhagen of the present position of diagnosis and treatment of some of the more important tumours and tumour like lesions of the eye and its adnexa

Key words eye tumours – ocular tumours – tumour diagnosis – tumour therapy – Ophthalmological Tumour Centre

It is a great honour for me to be the first Dane to deliver a Bjerrum lecture to the Danish Ophthalmological Society and especially on the occasion of its 75th anniversary The founder members of the Society formerly called The Ophthalmological Society of Copenhagen were Jannik Bjerrum Edmund Hansen Grut Edmund Jensen and K K K Lundsgaard (cit Lottrup Andersen 1952) We are greatly indebted to these men and to all our predecessors in ophthalmology

The choice of subject for this lecture is inspired by the close cooperation over many years between the Eye Pathology Institute in Copenhagen and Danish ophthalmologists

Eye pathology has been carried out in the laboratory of the eye department of Rigshospitalet since 1910 In 1941 a centralization of all eye pathology in Denmark at this laboratory was proposed by the late Professor Henning Ronne whose work I took over in 1946

The Tenth Bjerrum Lecture in the Danish Ophthalmological Society January 1976



Fig 1
Jannik Petersen Bjerrum
*26 12 1851 †2 1920
The first Chairman of the Danish Ophthalmological Society
Painting by Mathorn in the Eye Department
of the University Hospital Rigshospitalet Copenhagen
(from H Ehlers 1966)

It gradually became customary to send patients with suspected ocular tumours to the Eye Pathology Institute for clinical examination and as a consequence of this an Ophthalmological Clinical Tumour Centre was established at the institute in 1964 Ry Andersen (1965) Gregersen (19[illegible])

Since that time diagnostic and therapeutic advice has been given on more than two thousand patients from all parts of Denmark The practising ophthalmologist s opportunities for tumour diagnosis and treatment vary a great deal depending upon his situation There is an enormous difference between the opportunities of the lonely oculist among millions of people in a developing country and his well equipped Danish colleague but even the latter can arrive at more far re[illegible] decisions in an eye department than in his own private

office partly because of the technical facilities and partly because of the greate moral support a hospital department can offer in many situations The same holds true for the Ophthalmological Tumour Centre whose efforts often involve taking on a grave responsibility

I shall try to strike a balance between the too hackneyed and the too sophisticated My basis will mainly be what a Danish ophthalmologist can do in his own office and to what extent he must rely on the more refined register of hospital service

No systematic histopathological interpretation is intended in this paper The reader is referred to Histological Typing of Ocular and Adnexal Tumour World Health Organization Geneva which is expected to be in print at the end of 1976

Intraocular Tumours

Malignant melanoma

In Denmark the most common primary malignant intraocular tumour is the malignant melanoma of the uvea with about 40 new cases each year in a population of five million

O A Jensen showed in his thesis from the Eye Pathology Institute in 1963 that this is a very high relative frequency compared with other countries and that the malignant melanoma of the uvea is significantly more frequent in blue eyed than in brown eyed Danes In non whites malignant melanomas (of any kind) are rarer than in whites Among the different types the Knapp Rønne type of malignant melanoma of the choroid has a Scandinavian tradition (cit O A Jensen (1976))

The diagnosis of a malignant melanoma in the choroid or ciliary body is still difficult in its early stage I strongly recommend transillumination and especially retroillumination Reese & Jones (1957) Reese (1963) in addition to routine examination by ophthalmoscope Rhuby lens and three mirror prism We use a cold fibre light, introduced by Møller (1967) Sørensen (1975) most often transmitted through the eyelids by a specially constructed curved light source The examiner s eye is very close to the patient and sometimes provided with a prismatic magnifying glass In this way even small shadows in the area of the macula and the disc are easily noticed for example an incipient senile macular degeneration and their position in the retinal layers are often better evaluated than by use of the ophthalmoscope But retroillumination has to be used with caution it can be misleading and fallible

We often make drawings of the findings by ophthalmoscopic examination and by retroillumination and we find it more exact than retinal photographs (even

in infrared light) in establishing the most important symptom of a tumour - the steady growth

Incidentally an excellent description of the technique of transillumination was given in this Society in 1905 by Edmund Jensen, grandfather of our present Chairman Jens Edmund

Biopsy of intraocular tumours Ry Andersen (1954) is too dangerous except for iris lesions or in special cases for example one eyed patients. Jensen & Ry Andersen (1959) Jensen (1970)

Among our new aids fluorescein angiography gives valuable information on the vascularization of the lesion suspected Ultrasonic examination, which was introduced in Denmark by J Falbe Hansen and has been skillfully used during recent years by H Fledelius (1973) is a great help in differentiating between serous detachment and a solid lesion provided a prominence of 4-5 diopters or more is present. It is a particular help if cloudy media are present. In very flat lesions the use of ultrasonics and radioactive tracer methods are useless.

If there is doubt about the diagnosis it is wise to observe the patient this more conservative attitude was introduced in Denmark by H Ehlers 50 years ago Flocks et al (1955) and later O A Jensen (1963) have shown that the prognosis is not significantly worsened if very small choroidal malignant melanomas especially in elderly persons are observed until growth has been established

We have succeeded in this way in cutting down the percentage of enucleations for malignant uveal melanomas not confirmed histologically from 22 per cent to less than 5 per cent Ry Andersen (1970) Sometimes however we feel that we have observed patients for an unnecessarily long period especially at the Ophthalmological Tumour Centre For the time being the long term results of this procedure cannot be determined on the basis of our present material O A Jensen (1970b)

It is sometimes difficult to distinguish between a primary and a secondary uveal tumour As stated by Bjerrum (quoting Uhthoff) in our Ophthalmological Society in the year 1900 choroidal metastases are often flat and more disseminated than the primary ones which are solitary and more prominent Even in the event of a primary malignant tumour elsewhere, an intraocular tumour most often turns out to be a primary malignant melanoma, but the possibility of a metastasis of one or both eyes must always be kept in mind Godtfredsen (1944) Jensen (19 0a) With irradiation and steroid therapy the patients vision can often be preserved during the last hard months of their lifetime Uveal metastases from mammary carcinoma react better than metastases from bronchogenic carcinoma

Over hasty enucleation must be avoided. The problem is also topical in other

tumour like lesions especially in disciform macular degenerations I usually say Let me see the other eye first

The local eye department is usually able to establish the correct diagnosis In doubtful cases it is a help to allow more ophthalmologists to see the patient under continuous observation and the Ophthalmological Tumour Centre of the Eye Pathology Institute is always close at hand for the Danish ophthalmologist

Therapy is at present enucleation in most malignant melanomas of the choroid and ciliary body Some of the malignant melanomas of the choroid seem to be rather radiosensitive especially small and flat ones which sometimes can be destroyed by a radioactive 60 Cobalt applicator sutured to the sclera Stallard (1973) Perhaps this treatment should be used more often instead of enucleation e g in elderly patients Photocoagulation has been shown to be a disappointment A special diet without tyrosine and phenylalanine and with reduction of copper has been used by Edmund et al (1974) in two cases of one eyed patients and appears to be promising

It is still not clear how active the surgeon should be if examination of the enucleated eye demonstrates tumour growth outside the globe We usually advise extirpation of the surrounding orbital tissue but rarely exenteration of the orbit In these cases as always humanity is necessary advanced age or other conditions endangering life allow the ophthalmologist to be more conservative in his therapy

It is well known that melanomas of the iris are less malignant than other uveal melanomas If they are small and do not involve the chamber angle iridectomy is often sufficient If histopathological examination of the tissue removed demonstrates growth along the excised edge iridocyclectomy or enucl ation is indicated

Autoimmune reactions are undoubtedly noticed in uveal melanomas Rahi (1971) which may perhaps explain the rare spontaneous regressions reported O A Jensen & Ry Andersen (1974) For the future the field of immunology appears to be highly promising in cancer therapy also in relation to uveal malignant melanomas

Retinoblastoma

In Denmark retinoblastoma is second in frequency among primary intraocular tumours with an incidence of 1 18 000 births i e five cases per year (one case per million) One third of these are bilateral Jensen (1965 1968)

According to Warburg (1974) one type of retinoblastoma is inherited as an autosomal dominant trait the other type arises as a somatic mutation All bilateral cases are heritable and also about 15 % of the unilateral cases It has been suggested that retinoblastoma is more common in non whites but recent

reports do not support this Warburg (1974) Devesa (1975) Histopathologically there is only a difference by degree between undifferentiated and differentiated retinoblastomas with Flexner Wintersteiner rosettes or fleurette like abortive photoreceptor arrangements Tso et al (1970) There are many intraocular tumour like lesions which have to be distinguished form a retinoblastoma O A Jensen & Kleener (1971)

Mullaney (1969a b) has suggested the likelihood of circulating anti DNA antibodies in retinoblastoma patients and a possible antigenic role for retinoblastoma tumour cells particularly in cases of spontaneous regression Spontaneous regression with necrosis is a very rare event In one such case we demonstrated necrosis of the central retinal vessels Ry Andersen & O A Jensen (1974)

The retinoblastoma is highly radio sensitive and radio curable In Denmark until now the first eye has most often been removed for histopathological examination and the second treated by radiation which is centralized at the Radium Centre and the Department of Ophthalmology University of Århus Ehlers & Kaae (1975)

There is no doubt that in the future retinoblastomas in one eye or in the first eye in bilateral cases will also be treated by radiation provided they are detected early enough

I strongly recommend that all Danish patients with lesions suspected of being retinoblastomas and which are small enough for radiation treatment primarily should be directed to the Department of Ophthalmology at Århus

Present day radiation treatment is often by means of radioactive applicators introduced by Stallard in 1948 by shell shaped discs (Stallard discs) or Rosengren & Tengroth s platinum balls (1963) External radiation is used with success by among others Hyman et al (1968) using megavolt X ray treatment of the whole retina and vitreous with shielding of the anterior part of the eye often combined with cytostatic agents (TEM) Even though the megavolt treatment very often causes a cataract I personally prefer this type of radiation Ry Andersen (1969) The small amount of material available in Denmark makes it difficult to obtain the experience necessary In 1969 I proposed centralization of radiotherapy of retinoblastoma on a Scandinavian level at Århus or Goteborg Ry Andersen (1971b) The time for this does not yet appear to have arrived but I still believe that centralization in Scandinavia will in many cases save vision and life

Enucleation for retinoblastoma is technically not an easy task A long optic nerve of about 15 mm is often of vital importance since retinoblastoma first proceeds along the optic nerve as already stated by Linde (1875) No other eye operation has such fatal consequences as this if incorrectly performed



Fig 2

Malignant medulloepithelioma from posterior retina and optic nerve Case from 1894 originally considered by Bentzen as angioma of optic nerve (Eye Path Inst No 180 65 reduced from × 125)

Medulloepithelioma of the retina

Except for the common naevi in the uvea intraocular tumours other than the above mentioned are rare Even so I cannot finish this section without mentioning my favourite tumour Medulloepithelioma (formerly called diktyoma) Ry Andersen (1948 1959 1962 1971a) Zimmerman et al (1972)

Medulloepithelioma of the retina is an embryonal tumour most often arising during embryonic development of the ciliary epithelium Histopathologically its appearance is variegated but characteristic The teratoid form may in addition contain tissues imitating cerebral glia ependyma choroid plexus ganglion cells and cartilage We recently demonstrated rhabdomyosarcomatous differentiation in these tumours Zimmerman et al (1972)

Ten years ago on clearing out some old material in the Eye Pathology Institute I found an old specimen labelled angioma of optic nerve Bentzen Heidelberg 1894 The Danish Ophthalmologist Chr Bentzen visited the famous eye clinic in Heidelberg in 1894 and he must have brought the slides home They show a malignant medulloepithelioma from the posterior retina and optic nerve (Fig 2) The features and the location are the same as those demonstrated

by Reese in 1957 Many years ago the two famous ophthalmic pathologists Verhoeff of Boston and Fuchs of Vienna fought a formidable battle over the priority of the first cases of medulloepithelioma Verhoeff (1904) Fuchs (1908) Zimmerman (1971) They should have known that a much older case with a still more rare location laid hidden at the bottom of a cupboard in a Danish hospital The case has never been recognized as a medulloepithelioma (diktyoma) and I have been unable to trace the origin neither in Copenhagen nor in Heidelberg

I took advantage of the opportunity to mention this historical case in the Festschrift in honour of one of the pioneers of clinical ocular tumour research my friend A B Reese of New York Ry Andersen (1971a)

Tumours of the Orbit

Few diseases make more demands on clinicians and eye pathologists than orbital tumours and tumour like lesions A very broad spectrum of benign and malignant neoplasms malformations cysts and inflammatory lesions must be considered For details the reader is referred to the Proceedings of the Second International Symposium on Orbital Disorders Bleeker et al (1975)

The most frequent clinical manifestation of an orbital lesion is proptosis and the most common cause of proptosis whether bilateral or unilateral is endocrinopathic (e g Graves Basedow disease) Except for these cases biopsy is usually of crucial importance for differential diagnosis before therapy can be instituted

As a result of the pilot investigation by Eldrup Jorgensen (1970) and the experience of the Eye Pathology Institute the number of primary histologically verified orbital tumours in Denmark is estimated to be about 20 a year i e four to each one million inhabitants According to Eldrup Jorgensen & Fledelius (1975) and Fledelius (1976) one fifth of these occurs in children and of these about one quarter are malignant most often embryonal sarcomas or rhabdomyosarcomas

The number of clinical tumour like orbital lesions without histological verification is not known but it is estimated to be larger than the real neoplasms Among the tumour like lesions a sequel of thyroid disease is a possibility Ry Andersen et al (1963)

Embryonal sarcoma and rhabdomyosarcoma

Orbital sarcomas in children have been found to be quite radio sensitive and in a fair number of cases they are radio curable In Denmark we try to centralize these sarcomas and lesions suspected of being sarcomas in children on a national level in a team the Eye Pathology Institute s Tumour Centre acting as co ordinator involving the Radium Centre of Copenhagen and departments in ophthalmology pediatrics plastic surgery neurosurgery and maxillary surgery at the Rigshospital Early diagnosis is crucial – we advise ophthalmologists to send in these children as early as possible preferably without biopsy The first step is ultrasonography Fledelius (1975) and EMI scanning of the orbit and the second is biopsy preferably from the anterior route without lesion of periosteum In addition tomography of the orbit and pediatric examination including haematologic studies are undertaken

When the diagnosis of an orbital sarcoma is established histopathologically treatment in Denmark consists for the time being of megavolt radiation up to 5-6000 rad tumour dose synchronous with immunosuppressive therapy If the tumour disappears satisfactorily during this treatment the immunosuppressive treatment continues for about a further six to twelve months under careful observation Exenteration of the orbit is performed if the tumour does not respond satisfactorily or in the event of recurrence This is in line with the present treatment at the University of Colombia in New York Ellsworth (1975) and at the Moorfields Hospital in London Lederman & Jones (1974) Wright (1975) The London group does not however use immunosuppressive treatment as a routine procedure

It is not intended to centralize all *benign* orbital tumours and tumour like lesions on a national scale in Denmark

Epithelial tumours of the lacrimal gland

The histological features are very similar to those of the salivary glands but in the orbit they often run a more malignant course This holds good for pleo morphic adenomas as well as for carcinomas of the lacrimal gland above all the adenoid cystic carcinoma One of the reasons for the more malignant be havoir of lacrimal gland tumours is probably the nearby location of periosteum and bone with a tendency towards invasion into these structures In addition surgery in the lacrimal gland region is often insufficiently radical The patients are usually rather young and even though they survive for many years recur rences and finally invasion into the cranial cavity is frequently the end result The treatment preceded by gentle biopsy is usually a combination of radio therapy and surgery Removal of periosteum in the region of the lacrimal gland

and resection of the bone may be necessary With this combined treatment the eye can often be saved I agree with Ashton (1975) that the vast majority of carcinomas require exenteration of the orbit and removal of all possibly in volved tissue In inoperable cases irradiation is the method of choice

Tumours of the optic nerve

The histological structure of the optic nerve is that of a myelinated white fibre tract *surrounded by typical meningeal tunics Its tumours* are therefore similar to those of the central nervous system The tumours of the optic nerve itself are nearly always benign pilocytic astrocytomas (gliomas) in children

A few highly invasive astrocytomas may be encountered especially in the vicinity of the chiasm

In a Danish material 50 per cent of optic nerve astrocytomas (gliomas) ex hibited more or less pronounced symptoms of Recklinghausen s disease Christen sen & Ry Andersen (1952)

Astrocytomas of the optic nerve are rather radiosensitive especially in the region of the chiasm

Meningiomas from the sheaths of the optic nerve arise from the arachnoidal tunic and most of them are of the endotheliomatous type They are seen in adults and are characterized by reduction of movement of the eye but vision is retained for a long time in contrast to optic nerve astrocytomas

Lymphoid orbital lesions

Lymphoid orbital lesions differ from lymphoid lesions elsewhere As emphasized by Kleener (1975) this may perhaps be due to the fact that lymph nodes or functioning lymphatic vessels have never been proved to exist in the orbit This anatomic peculiarity was already suggested by my formed principal in ophthalm ology C F Heerfordt in this Society in 1904

Histopathologically the lymphoid tumours and tumour like lesions may be divided into three broad categories 1) reactive lymphoid hyperplasia (lymphoid pseudo tumour) 2) lymphoid lesions of indeterminate nature and 3) malignant lymphoma and leukaemia

The intermediate group the lymphoid lesions of indeterminate nature in cludes macroglobulinaemia (Waldenstrom s disease) and other dysproteinaemias associated with lymphoproliferative disease PAS positive intranuclear Dutcher Fahey bodies are frequently found It is often impossible for the pathologist to distinguish with certainty between these groups A long period of observation

with repeated clinical examination will often reveal the presence of a generalized malignant disease in haematopoietic or lymphoid tissue in some cases the orbital growth being its first manifestation Kleener (1976) It may be hoped that immunological research will in the near future clear up the uncertainty and become an aid in classification and therapy James (1974) For the time being radiation in tumour doses is the method of choice in most cases

Tumours of the Lacrimal Drainage System

Rarely the lacrimal drainage system may harbour tumours including papillomas and carcinomas both of squamous cell or transitional type The diagnosis of these tumours is made by the ophthalmologist but in Denmark treatment is performed in collaboration with otorhinolaryngologists

Tumours of the Eyelid

By far the greater part of tumours of the eyelid are benign about 90 % according to Bech & O A Jensen (1976) The ophthalmologist can easily make an excision or have this performed at the nearby ophthalmological department If there is suspicion of a carcinoma we advise open biopsy without suture or reference of the patient to a larger eye department one of the Radium Centres or the Ophthalmological Tumour Centre of the Eye Pathology Institute Open biopsy without suture can easily be performed as a deep excision with a knife from the edge of the lesion including non necrotic parts of the tumour and the surrounding tissue Open biopsy is far preferable to an nonradical excision for the following reasons 1) Nonradical excision without further therapy is dangerous 2) if radiotherapy is used it is often impossible one to three weeks after the surgical excision for the radiotherapist to assess the size and location of the original tumour Radiation must often be postponed for several months or a larger radiation field must be used which means that the scar following the radiation will be more disfiguring and the risk of ectropion or other complications is greater 3) in addition a large scar after the operation will give a reduced response since the cancericidal effect of the radiation is largely dependent upon a sufficient oxygen supply i e an intact stroma with intact blood vessels is an important factor Curettage is not suitable on the eyelid Reymann (1971 1973) where a firm support is difficult to obtain

Lesions suspected of being melanomas in the eyelids should not be biopsied in order to avoid risk of spread and metastases In such cases referral of the patient to a plastic surgical department or the Ophthalmological Tumour Centre is advised The plastic surgeon will often perform a localized extirpation with a small border of healthy tissue The microscopy will be decisive In the event of a malignant melanoma plastic surgical removal must be performed as quickly as possible in ample healthy tissue i e one and a half cm of healthy tissue on all sides and at the bottom Malignant melanomas of the skin including the eyelids are radio resistant

For comparison a squamous cell carcinoma demands as a minimum one cm of healthy tissue and a basal cell carcinoma 0 5 cm If these rules are followed carcinomas of the eyelid can be treated surgically with results as good as radia tion therapy In many countries such as the United States and Great Britain most carcinomas of the eyelid are treated by plastic surgeons with good results e g by Mustarde in Glasgow (1974)

As a former radiotherapist I myself have always been fascinated by radio therapy Ry Andersen (1949) This is due to the high level of radiotherapy in Denmark over many years and the personal inspiration of my old teacher at the Radium Centre of Copenhagen the late Jens Nielsen

According to a follow up at the Radium Centre in Copenhagen by Johansen (1976) 97 per cent of all carcinomas of the skin treated by radiotherapy were cured without recurrence after five years of observation If referred to the Radium Centre in good time nearly 100 per cent can be cured by proper radia tion treatment According to Johansen the Meibomian carcinomas appear to have the same prognosis as the basal cell carcinomas but they demand radiation at a somewhat higher voltage

Tumours of the Conjunctiva

Carcinomas of the limbus are usually fairly inoffensive and a biopsy or non radical excision followed by radiation treatment with Strontium^{90} is usually enough for permanent cure with good cosmetic results

We advise that benign naevi be removed in healthy tissue without biopsy Congenital melanosis of the conjunctiva is a benign lesion The acquired intra epithelial melanoses are pre cancerous and radio sensitive They demand close observation sometimes over many years If they show signs of growth with

formation of nodules we advise excision of one of the nodules for microscopy In some cases but by no means in all a malignant melanoma develops

Malignant melanomas of the conjunctiva may arise in junctional or compound naevi in intraepithelial melanosis or *de novo* The last category appears to have the worst prognosis

Conjunctival malignant melanomas at or near the limbus are radio sensitive and have a better prognosis than melanomas near the margin of the eyelids In the luckily quite rare cases of widespread malignant melanoma in the conjunctiva eventually including the eyelids one is forced to exenterate the orbit with removal of all conjunctival tissue and the eyelids

As always the ophthalmologist should try to be effective in his treatment without coming into conflict with the noble principle of the medical art Primum non nocere

The coming thing is cooperation about research diagnostics and treatment on a national as well as on an international level

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BLOOD AQUEOUS BARRIER IN NEWBORN AND YOUNG RABBITS

An electron microscopic study

BY

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and ARTO PALKAMA

Distribution of intravenously injected horseradish peroxidase (HRP) in the ciliary body of newborn and young (2 weeks old) rabbits was studied with the electron microscope
The reaction product was localized in all animals in the lumen of the blood vessels in the perivascular area in the surrounding connective tissue stroma and also in the epithelial cell layers The peroxidase penetrated through the intercellular junctions of the pigmented cells to the inter cellular space between the apical membranes of the two epithelial cell layers In young rabbits peroxidase penetrated between the apical inter cellular clefts of the non pigmented cells in small quantities only whereas in the newborn animals the clefts were filled with peroxidase This reflects differences in the blood aqueous barrier mechanism between the two studied groups and is evidently due to developmental stages of the eyes

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A comparison of aqueous humour in young and in adult rabbits has shown that the composition of the aqueous humour changes during development (Wessely 1923 Kinsey Jackson & Terry 1945 Kinsey & Jackson 1949 Davson 1969a) The penetration of various drugs into the aqueous humour varies with the age of the developing eye (Kinsey & Williamson 1949 Davson 1955)

An important function of the different cell structures of the ciliary epithelium is probably the prevention of the free passage of numerous substances from the capillaries of the ciliary body into the posterior chamber This barrier mechanism has been studied with exogenous tracers (Smelser & Pei 1965 Shiose 1970 Smith 1971 Vegge 1971 Uusitalo Palkama & Stjernschantz 1973)

The aim of the present study was to investigate the blood aqueous barrier system in the developing eye The technique of an intravenous injection of horse radish peroxidase (Graham & Karnovsky 1966a) was used to evaluate the penetration of protein molecules through the ciliary epithelium Newborn and young (2 weeks old) rabbits were used to correlate the morphological changes of the ciliary body with biochemical and physiological changes of the aqueous humour due to maturation of the barrier system

Materials and Methods

A total of 13 albino rabbits was studied One group of animals (4 rabbits) was one day old and another (9 rabbits) was 14 days old The animals were anaesthetized with 0 1–0 2 ml of an aqueous solution of pentobarbitone sodium (20–40 mg/kg) injected intraperitoneally In all experimental animals an intravenous injection of horseradish peroxidase (HRP) (type II Sigma Chemical Company St Louis Mc) was used The rabbits were injected with isotonic saline (0 2–0 4 ml for newborns and 0 5–0 8 ml for young rabbits) containing 100–200 mg/kg bodyweight HRP A control group received a corresponding amount of pure isotonic saline

The experiments were carried out in two different phases so that each time one group of animals was injected with HRP one control an[illegible] injected with isotonic saline only The eyes of the newborn rabbits we[illegible] eitl 10 min or 30 min after the injection The eyes of the your[illegible] cleated 3 min 10 min or 30 min after the injection of the [illegible] ls newborn rabbits were gently opened and lateral [illegible] performed before the enucleation Both eyes v[illegible] and vitreous were removed and each cilia[illegible] te ring and sectioned into small blocks

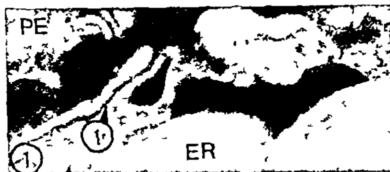


Fig 1
Black reaction product around erythrocytes (ER) in the lumen of a capillary from a young rabbit Staining is seen in the intercellular clefts (arrow 1) HRP reaction product is also seen in the stroma (S) surrounding the capillary PE indicates pigmented epithelium × 25000

Most of the eyes were fixed by immersion in a 2 5 % glutaraldehyde formal hyde mixture in 0 1 M cacodylate buffer pH 7 2 The eyes of two young rabbits were fixed before enucleation by perfusion 10 or 30 min after injection of HRP and then fixed as above Perfusion fixation was performed by injecting a mix ture of glutaraldehyde formaldehyde (Karnovsky 1965) through the heart at a pressure of about 120 cm H_2O (Rechardt 1969)

After fixation all the samples were washed overnight in 0 1 M phosphate buffer pH 7 2 at 4 C and the tissue blocks were then incubated for 30 min at room temperature in the 3 3 diaminobenzidine and H O medium favoured by Karnovsky and his associates (Graham & Karnovsky 1966a Graham & Karnov sky 1966b Karnovsky 1967 Schneeberger Keeley & Karnovsky 1968) The spe cimens were embedded in Epon Araldite sectioned and half of them were double stained and studied under a Philips EM 300 or Jem 100B microscope

Results

Tissues from HRP injected animals examined under the electron microscope showed a black granular precipitate which indicated the enzyme reaction pro duct This was localized both in newborn and young rabbits in the lumen of the blood vessels (Fig 1) in the perivascular area (Fig 1) in the connective tissue of the stroma (Figs 1 4) and also in the epithelial cell layers (Figs 2 3 and 4)



Fig 2

Electron micrograph from ciliary epithelium of a newborn rabbit Reaction product can be seen in the apical pole of the intercellular space (ICS) of two adjoining non pigmented epithelial cells (NPE 1 and NPE 2) PC indicates posterior chamber and LI lateral interdigitation × 42000

Fig 3

Higher magnification of the same intercellular space seen in Fig 2 White arrows indicate HRP reaction product dark intercellular space devoid of reaction product × 16?000



Fig 4

HRP reaction product in the ciliary process of a young rabbit HRP has freely diffused through the intercellular spaces of the pigmented epithelium (PE) and is also seen at the apical intercellular space of the two epithelial cell layers Some intercellular junctions between the pigmented (PE) and non pigmented (NPE) epithelial cells are unstained (arrows 1 and 2) Some of the intercellular junctions seen around fingerlike projections of adjacent cells which have been cut in cross section are totally or partly filled with reaction product as can be seen in the insert (arrow 3) Posterior chamber is marked PC ciliary channel CC basal infoldings BI and stroma S
× 11000 (insert × 30000)

Both in newborn and young animals it was possible to find small blood vessels in which the reaction product seemed to outline the entire intercellular clefts between adjacent endothelial cells (Fig 1) There appeared to be *no clear cut* differences in the endothelial staining of newborn and young rabbits

In the epithelial cell area of the ciliary body the reaction product was clearly visible in the elaborate infoldings of the basal and lateral cell membranes of the pigmented epithelium (Fig 4) The intercellular space between the apical membranes of the two epithelial cell layers was also usually filled with the precipitate (Fig 4) The intercellular junctions (zonulae adherentes and partly zonulae occludentes) at the apical poles of the non pigmented and pigmented epithelium were also stained (Fig 4)

The penetration of HRP was not totally blocked by the non pigmented epithelium In newborn rabbits the reaction product could be seen in the apical pole of the intercellular space of two adjoining non pigmented cells (Figs 2 and 3) The heavy staining was also occasionally seen at the basal part of the intercellular space in the non pigmented cell layer and at the internal limiting membrane both in newborn and young rabbits (Fig 5)

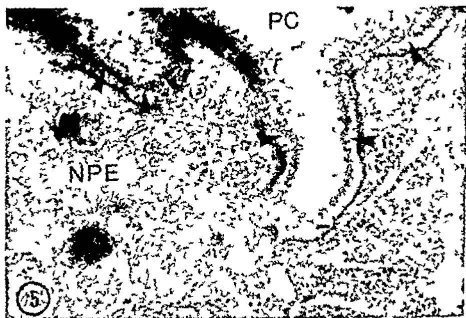


Fig 5

Heavy staining (arrows) at the internal limiting membrane in the eye of a young rabbit Posterior chamber is marked PC and non pigmented epithelium with NPE ×55000

In newborn rabbits there is a shortage of interdigitations of the non pigmented epithelium In young rabbits the basal and lateral interdigitations of the non pigmented epithelium are well developed suggesting maturity of the epithelial cells (Fig 4) In spite of these morphological differences between one day and two week old rabbits the junctional complexes at the apical regions of the non pigmented cells seemed morphologically similar Penetration of the tracer at the apical intercellular clefts between non pigmented cells was however more pronounced in newborn rabbits than in two weeks old rabbits (Compare Figs 2 and 4)

Apart from the intercellular localization of the reaction intracellular vesicles were sometimes seen which seemed to contain the reaction product These were usually found at the apical pole of the non pigmented cells The frequency of these vesicles 30 min after HRP injection had clearly increased They were however never seen at the basal pole of the non pigmented cells

Discussion

The two layers of the ciliary epithelium are supposed to possess functional differences This has been based on electron microscopical electrophysiological and histo and biochemical investigations (e g Davson 1969b Cole 1970) These reported findings indicate a higher metabolic and secretory activity in the non pigmented cells (Shimizu Riley & Cole 1967 Russmann & Heisig 1972)

A special role of the non pigmented cells is their possible counterpart in the complex called the blood aqueous barrier (Shiose 1970 Smith 1971 Vegge 1971 Uusitalo Palkama & Stjernschantz 1973) Vegge (1972) suggests that the junctional complexes at the apical pole of adjacent non pigmented cells in the ciliary epithelium of monkeys form the blood aqueous barrier system to proteins It is difficult to explain what makes these particular junctions of the non pigmented epithelium so effective a barrier because the pigmented cells are sealed together with similar tight junctions even more frequently than the non pigmented cells (Bairati & Orzalesi 1966)

The present study provides evidence for the prominent role from the point of view of the blood aqueous barrier system played by the non pigmented epithelium in developing eyes The exogenous protein tracer (HRP) gains free access from the blood stream to the intercellular spaces in the postnatally developing eye It did not however pass much further than to the apical junctions of the non pigmented cells It was still possible to see the reaction product in almost all parts of the internal limiting membrane A penetration of the tracer

from the apical pole to the basal pole of the non pigmented cells could not be ascertained It seems however quite logical that at least some HRP really penetrated the junctions of the non pigmented cells The reaction product at the internal limiting membrane could also be due to post mortem diffusion from the intercellular spaces The possible role of the hyaloid system especially in the eyes of newborn rabbits should not be excluded in this connection

On the other hand the presence of the reaction product at the basal infoldings and internal limiting membrane in the two week old rabbits cannot be explained by presence of a hyaloid system since such a system should no longer exist at that stage of development Therefore the passage of HRP through the non pigmented epithelium seems most likely in these rabbits Vesicles containing the reaction product in the non pigmented cells were few in number It is quite evident that they cannot have been responsible for a transport of HRP to any great extent because firstly they were few in number and secondly they were never seen at the basal pole of the non pigmented cells So there remains the route through the junctional complexes of the non pigmented cells which HRP has evidently taken

The tight junctions at the apical portion of the non pigmented and pigmented epithelium are frequently found already after the 22nd day of gestation as shown by Weingeist (1970) The fine structure of these complexes in the non pigmented and pigmented epithelium seems to be very similar both in newborn and adult rabbits (Bairati & Orzalesi 1966 Weingeist 1970) However the junctions show different permeabilities HRP passes freely through the inter cellular spaces of the pigmented cells to the apical membranes of the two epi thelial cell layers According to the results obtained in this work the junctional complexes between the non pigmented cells both in newborn and young rabbits are at least partly permeable to HRP as indicated e g in Fig 4 In this figure the reaction product can be seen between adjacent non pigmented cells as well as at the internal limiting membrane

Although no clear cut morphological differences could be observed between the fine structure of the newborn and young rabbits it was found that HRP had an easier passage between non pigmented cells in the newborn than in the young rabbits This points to a difference in their barrier systems which evi dently is under development during the period of age studied here

According to the present and earlier results it seems quite evident that the junctional complexes at the apical extension of the non pigmented cells play a most important role in the mechanism called the blood aqueous barrier both in newborn and young rabbits It is difficult to say what makes these particular junctions different from other morphologically similar junctions e g the junctions between the pigmented cells The quantitative and qualitative superio

rity in metabolic processes of the non pigmented cells as compared with the pigmented cells (Russmann & Heisig 1972) makes it evident that metabolic factors also probably play an important role in the effectivity of the junctions between the non pigmented cells

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RESEMBLANCE BETWEEN TONOMETER READINGS ON RELATIVES AND SPOUSES

BY

BO BENGTSSON

The resemblance between tonometer readings on relatives and spouses was studied in a material derived from a population survey and consisting of 1042 unique individuals forming 365 nuclear families and 1333 pairs divided into groups with different sex composition and type of connection Persons in whom glaucoma was suspected were excluded The general level of resemblance in the present study was similar to that in previous studies Differences between groups with different sex composition conformed to a pattern expected from environmental effects The resemblance between husbands and their wives was highly significant and of the same order of magnitude as that in relatives sharing a common genetic background We concluded that a common environment contributes materially to the re semblance between tonometer readings on relatives The possibility of a cumulative environmental effect was suggested by an increase in resem blance with age

Key words population study – intraocular pressure – applanation tono metry – inheritance – environment

Armaly (1965 1966 1967) and Armaly et al (1968) reported that the ocular pressure level is genetically determined in the normal eye Levene et al (1970) considered themselves able to confirm a significant heritability for ocular ten

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sion A comparison between the results of Levene et al and those of Armaly et al was alleged however to indicate a disparity – possibly reflecting a true difference in heritability between different populations with different environ ments The present study of the resemblance between tonometer readings on first degree relatives therefore seemed appropriate as part of an attempt to assess different source of variation in a native population

The phenotypic (total) variance V_P of a metric (quantitative) character P is usually regarded as consisting of separate causal components (effects) $V_{P\,K}$ $V_{P\,L}$ $V_{P\,M}$ etc attributable to sources of variation (factors) K L M etc with variances V_K V_L V_M etc of their own

The effects of mutually uncorrelated factors are additive

$$V_P = V_{P\,K} + V_{P\,L} + V_{P\,M}$$

Interactions can usually be removed by suitable transformations of scale and will not be discussed further

A simple regression analysis suffices to determine the linear effect $V_{P\,M}$ of a mea surable factor M which is uncorrelated to other sources of variation

$$V_{P\,M} = b_{PM} V_M = r_{PM} V_P$$

(b = regression coefficient r = correlation coefficient)

A multiple regres ion analysis is needed to assess the combined effect $V_{P\ \ p}$ of several measurable but mutually correlated sources of variation

$$V_{P\,exp} = R\,V_P$$

(R - multiple correlation coefficient)

Many sources of variation are themselves inaccessible to measurement Their effects *can nevertheless be revealed by simple measurements of phenotypic values* – provided that it is possible to divide the population into groups consisting of individuals inde pendently inferred to be equally influenced by the factor under consideration The members of such groups covariate i e the variance between such groups is larger – and within groups smaller – than expected from pure chance In theory the covariance of phenotypic values would be equal to the effect of the concealed factor In practice however the grouping of the population can seldom be made totally independent of all pertinent factors but one In accordance with the method chosen to divide the popula tion into groups causal components therefore have to be estimated in a more indirect way which requires knowing how they contribute to the covariance The covariance of relatives for instance is composed of effects caused by dominance and common en vironment as well as of additive genetic effects

$$cov_P sibling_P sibling = V_{P\,c\ \ nv} + \tfrac{1}{2}V_{P\,addg\,n} + 1/4\,V_{P\,dom}$$

$$cov_P offspring_P parent = V_{P\,com\ \ n} + \tfrac{1}{2}V_{P\,addg\,n}$$

In a population divided into pairs rather than larger groups a simple regression analysis is again the method of choice It should be appreciated however that this time the regression (or correlation -) coefficient itself – not its square – should be used to determine the effect of the common sources of variation

$$cov_P dep_P indep = bV_P indep = r\sqrt{V_P indep\ V_P dep}$$

The covariance is in fact often expressed as a proportion of the phenotypic variance that is as the regression (or correlation –) coefficient

Within our own species this type of analysis is performed intuitively – resulting in an instantaneous recognition of the phenomenon known as resemblance between simi larly affected persons e g relatives

Material

The material was derived from a general ophthalmic population survey which was carried out at the Dalby Health Centre in southern Sweden from March 1969 to April 1970 Invitations with a brief questionnaire were mailed in rota tion following a directory to all persons aged 8 years or more who had been resident in the village surrounding the Health Centre since December 1968 Out of 1917 persons invited 1702 (88 8 %) took part in the study

Information about persons who failed to turn up or in whom the examination was incomplete has been given in earlier reports (Bengtsson 1972a b 1973)

Twenty cases subject to antiglaucomatous treatment lesions in the anterior chamber angle active uveitis or glaucomatous field defects were excluded from the present study

The official identification numbers of the eldest sibling and the eldest child of each person were requested in the questionnaire and orally verified at the examination (In Sweden every inhabitant has his own person number con sisting of ten figures – birth date birth number and control number – and more or less universally used for the purpose of identification in all types of official registers) Using those data 365 nuclear family groups consisting of 1042 unique

Table I
Number of families with different compositions

Type of family	Number of children 1	2	3	4	5
Mother father and offspring	117	70	23	3	1
Mother and offspring	40	21	3	2	0
Father and offspring	19	8	2	0	0
Siblings	–	49	7	0	0

individuals were (subsequently) assembled and pairs of first degree relatives and spouses constructed as detailed later The composition of families is shown in Table I

Serological verification of the different types of first degree relations was not attempted

The method used here to establish different kinds of kinship is of course not infallible but was deliberately chosen because it was practical

In half sibships one of the two full sibships was only referred to the joint parent and the second full sibships only to the other parent In such cases the fact that the parents had children in common was obscured It is also possible that a few halfsibs have been registered as full sibs even if the children in the older full sibship often retained their original surname when following their mother into a second marriage The degree of interrelationship on the other hand has been underestimated in monozygotic twins and persons with multiple relationships A previous very comprehensive study (Essen Moller 1967) of familial interrelatedness and consanguinity in a population partly identical with the present one admits of the conclusion that errors caused by the concise registration of relatives are few and therefore of little or no consequence

In comparison with collection of data pertaining to ancestors the present procedure has several advantages that are worth mentioning It is easier for parents to state the identification numbers of their children than vice versa Involvement of persons not alive and/or not investigated was minimized Discussions of illegitimacy were avoided It was possible to abbreviate the procedure for people lacking children and/or siblings

It should be appreciated that one person may be a member of two nuclear family groups and/or may appear both as child and sibling in one of those (Table II) Three six or ten pairs of siblings can be formed in families with three four or five children

Age and sex distributions are given in Table III Table IV shows the distribution of applanation pressures in the present material

Table II
Types of first degree relationships formed by 1042 *unique individuals*

Type of relation	Number of individuals
Parent	440
Child	158
Sibling	66
Parent and child	18
Parent and sibling	53
Child and sibling	295
Parent child and sibling	12

Table III
Age and sex distributions

Age (years)	Fathers	Mothers	Sons	Daughters	Brothers	Sisters	Males	Females
0– 9	0	0	43	36	25	17	44	38
10–19	0	0	127	124	99	93	129	125
20–29	0	9	58	34	45	27	64	46
30–39	68	98	20	13	16	11	84	105
40–49	84	85	6	11	14	16	89	90
50–59	48	46	5	4	10	8	54	53
60–69	36	25	1	1	11	9	44	32
70–79	5	11	0	0	6	15	10	23
80–89	2	5	0	0	1	3	3	8
90–99	0	1	0	0	0	0	0	1
Total	243	280	260	223	227	199	521	521
Mean age	47.8	45.7	18.4	18.3	24.7	27.9	33.3	34.9

Methods

Visual acuity ophthalmometry slit lamp examination Goldmann tonometry Schiotz tonometry sphygmomanometric measurements of the systemic blood pressure ophthalmoscopy in mydriasis subjective refraction in cycloplegia and fundus photography were attempted in every case Conventional equipment was used according to a fixed program

The applanation tonometry was performed by the author using a Goldmann tonometer mounted on a Haag Streit 900 slit lamp The tonometer was tested at PTB in Berlin and found to be completely devoid of demonstrable errors in the pertinent pressure range (For method see Jessen 1969) The right eye was always measured first *the instrument was read to the nearest millimeter* and the first reliable reading was recorded The arithmetic mean of the Goldmann readings on the two eyes was used to represent the intraocular pressure of the individual

All data were immediately codified and recorded on special forms Transfer

to punch cards and further processing were performed at the computer centre in Lund The analysis was carried out with a standard computer program – SPSS

Results

Several different final methods of analysis have been reported in earlier studies Initially we used both crude pressure readings and corrected pressures (Bengtsson 1972a) In both cases we calculated covariances and coefficients of regression as well as correlation coefficients

Table IV
Distribution of Goldmann readings

Goldmann readings	Number of individuals	
	Right eye	Left eye
5	1	1
6	0	0
7	1	0
8	7	7
9	18	15
10	36	38
11	70	61
12	134	133
13	153	157
14	150	146
15	157	154
16	131	131
17	97	101
18	41	49
19	24	29
20	16	17
21	1	1
22	1	1
23	2	0
24	0	1
25	0	0
26	1	0
27	1	0
Total	1042	1042

Correction of applanation pressures did not affect the results significantly or systematically and was therefore omitted In quantitative genetics the degree of resemblance between relatives is eventually used to predict the outcome of selective breeding In this situation parameters relating the covariance to the variance of potential parents of future offspring – i e heritability and/or coefficient of regression – are the natural choice For a more descriptive purpose like the present one the coefficient of correlation was considered to be equally adequate and more generally known as well as being more easily understood

In order to make different correlation coefficients directly comparable constructed variables such as the pressure of midparents and mean children were avoided All pairs therefore consisted of two individuals The part of the independent member of a pair was always assigned to the older relative and to the male spouse

Estimates of probabilities that observed correlation coefficients have arisen by chance were obtained from the standard computer program (SPSS) In Fig 1 the standard deviations were calculated according to the convention that SD of r = (1 r)/√n if the value of n is large and the value of r is small

Table V
Resemblance between tonometer readings on relatives and spouses

Pair members		Number of pairs	SD of indep var	SD of dep var	Correlation coefficient
independent	dependent				
mother	daughter	?11	2 37	2 3?	0 15 (P = 0 013)
mother	son	?31	2.39	2 24	0 2? ($P < 0\ 001$)
father	daughter	16?	2.57	2 30	0 0? (P = 0 263)
father	son	219	2 61	2 19	0 18 (P = 0 003)
sister	sister	64	2 47	? 32	0 41 ($P < 0\ 001$)
brother	brother	85	2 38	2 28	0 24 (P = 0 01?)
sibling	sibling of the other sex	144	2 3?	2 28	0 10 (P = 0 1?1)
sibling	sibling of the same sex	149	2 50	2 30	0 33 ($P < 0\ 001$)
mother	offspring	44?	? 38	2 31	0.20 ($P < 0\ 001$)
father	offspring	384	? 59	? ??	0 12 (P = 0 010)
parent	offspring	826	? ?0	? ?9	0 16 ($P < 0\ 001$)
sibling	sibling	?93	? 4?	2 ?9	0 ?2 ($P < 0\ 001$)
husband	wife	214	2 53	? 4?	0 22 ($P < 0\ 001$)

A certain degree of resemblance was observed in husband wife pairs as well as in parent offspring pairs and in pairs of siblings The correlation coefficients in those three major groups were all of the same order of magnitude and highly significant However great differences were obvious between the fundamental groups of relatives with a fixed sex in both members of the pairs Those latter groups are of course smaller and therefore subject to an increased random variation but the fact that the resemblances between fathers and their daughters and between siblings of different sexes were not at all significant while the correlations of mothers to their sons and between sisters were highly significant could not be disregarded The difference between the correlation coefficients in the two groups of parent offspring pairs mentioned was probably significant ($P < 0.05$ after z transformation) and the sex differences among siblings merit consideration even if their significance cannot easily be tested statistically since different groups of siblings are composed of the same individuals to such an extent that they have to be considered dependent on each other

As discussed later these findings suggested the possibility that a major part of the covariance of tonometer readings on relative might be caused by a common environment This situation was unforeseen at the outset of the present investigation Measurements suitable for testing preconceived hypotheses pertaining to the nature of such influences were lacking It seemed appropriate however to explore the present material

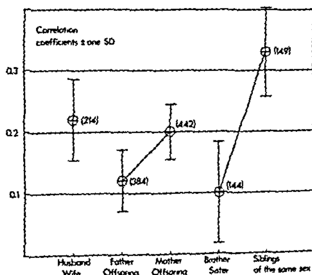


Fig 1

Dependence of degree of resemblance between relatives and spouses on type of relationship in the present material

in an effort to seek information that could be used to this end in the future. We therefore decided to look for effects of time and space as possible indicators of different environments

The time interval between pressure readings the age of the younger member and the residential addresses were used to construct new groups of pairs which were analysed in the same way as the original ones

If both members of a pair were measured within two hours the IOP readings were considered to have been made at the same time – otherwise not

The relevant entries in the directory used when mailing invitations were compared to settle the question as to whether both members of a pair lived at the same address or not

It was soon evident that the new parameters of selection were greatly dependent on each other Up to twenty years of age almost all children lived at the same address as their parents Adult men stayed on at their parental home much more frequently than women, and they were also much more frequently measured in the evening than were the women and children

The resemblance between pair members measured at the same time (r 0 18 n = 448) was only slightly greater than in pairs where the interval between measurements was longer (r = 0 14 n = 454) This comparison was made in all pairs of relatives living at the same address The mean age of the younger member was approximately the same in the two groups but fathers and daughters were more seldom measured at the same time – a fact that might well explain at least part of the difference It was concluded that the timing of applanations was of little importance in the present context

Similarly the importance of the residential address was investigated in parent offspring pairs where the younger member was at least twenty five years old Again a slight difference – between pairs living at the same address (r = 0.36 n = 42) and those living at different addresses (r = 0 30 n = 94) – might well be explained by the composition of the samples and/or by random variation The highest correlation coefficient in the present investigation (r = 0 50 n = 23) was however encountered when adults remaining at home after the age of twenty five were compared with their parents of the same sex

In parent offspring pairs the correlation coefficients increased from 0 15 (n = 579) via 0 20 (n = 111) to 0 32 (n = 136) when the age of the younger member rose from ≤ 19 via 20–24 to ≥ 25 years

Siblings of the same sex covariated to a greater extent if they were both younger than 16 (r = 0 42 n = 40) or older than 15 years (r = 0 32 n = 72) but less (r = 0 16 n = 35) if one was of compulsory school age and the other not Similarly siblings of different sexes tended to covariate only if both of them were (r = 0 12 n = 44) or were not (r = 0 15 n = 63) bound to attend school Oppositely sexed siblings on either side of the compulsory school age limit showed no such disposition (r = – 0 04 n = 37)

Discussion

The degree of resemblance between Goldmann readings on first degree relatives *in the present material depended on the sex of the two members in parent off* spring pairs as well as in pairs of siblings The disparities could not be explained by inheritance since the observed direction of the difference was opposite to that expected from the genetic correlations for sex linked characters in father daughter and father son pairs The great scatter of correlation coefficients in different sex combinations with the same degree of interrelatedness therefore strongly suggested the possibility of environmental influences

In this situation we had to decide which covariance was least likely to be augmented by an environmental component Generally speaking the correlation between fathers and their offspring is the most reliable from this point of view The correlation between mothers and their offspring is liable to give too high an estimate of the degree of inheritance on account of so called maternal effects The full sib correlation is least reliable The component due to common environ ment is often present in large amounts and the resemblance between relatives cannot be relied upon to do more than set an upper limit to the heritability (Falconer 1960)

Against this background the case for a significant degree of inheritance *seemed rather weak in the present material No significant correlation was* found when 165 daughters were compared with their fathers On the contrary the differences observed between fathers and mothers between parents and siblings and among siblings conformed to a pattern expected from environ mental effects

Perhaps most important of all the correlation coefficient in husband wife pairs was highly significant and of the same order of magnitude as those in relatives sharing a common genetic background This finding initially struck us as being contrasted to earlier studies reported to demonstrate clearly the complete independence of applanation pressure in husband and wife (Armaly 1966 1967 Levene et al 1970) On closer inspection correlation coefficients quoted earlier (Armaly 1966 1967) are found to be not only positive but *quite* substantial Their differences from the present one are not statistically signifi *cant ($P > 0\ 05$ after z transformation) and one of them is in itself significant* at the 5 % level of confidence ($r = 0\ 10$ n 419)

Salient features of the present study discussed so far are summarized in Fig 1 In short a resemblance between spouses possible maternal effects sex *differences in siblings and* small or insignificant correlations between fathers and their offspring led us to the conclusion that a common environment con tributes materially to the resemblance between relatives

A comparison of the present study with previous similar studies (Armaly 1966 1967 Armaly et al 1968 Levene et al 1970) shows that the actual values of the coefficients do not differ as much as the conclusions drawn from them (Figs 2 and 3) The nature of the problem requires that decisive importance should be attached to the lowest estimate of the resemblance between relatives – simply because any differences are more easily explained as being caused by changes in environment Concerning spouses on the other hand th possible existence of a resemblance cannot of course be ruled out by a failure to obtain significance for a positive correlation coefficient On the whole the salient features of the present study enumerated in the preceding paragraph could equally well be used to describe the composite material in Figs 2 and 3 Perhaps the difference between parents and siblings should be added At all events our original conclusion that a common environment contributes materially to the resemblance of relatives remained essentially unaltered

So far the discussion has centred on comparisons of *different groups within* the same study As mentioned in the introduction the general level of covariance has been alleged to differ in two previous investigations This opinion

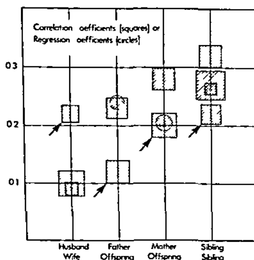


Fig 2

Dependence of degree of resemblance between relatives and spouses on type of relationship in the present and in earlier studies (Armaly 1966 1967 Armaly et al 1968 Levene et al 1970) The area of each square is proportional to the number of pairs in the respective group Arrows indicate observations belonging to the present study

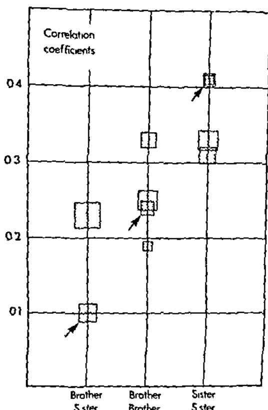


Fig 8

Dependence of degree of resemblance between siblings on sex in the present and in earlier studies (Armaly 1967 Armaly et al 1968 Levene et al 1970) The area of each square is proportional to the number of pairs in the respective group Arrows indicate observations belonging to the present study

however was based on calculations from regression coefficients that were incompatible since independent and dependent variables were interchanged The inclusion of the Twins Study of Armaly (1967) into the comparison also seems unwarranted Fraternal twins share a common environment to a greater extent than other full sibs and can be suspected of being more strongly correlated than ordinary siblings In fact some of the estimates of the heritability of intraocular pressure readings (up to 0 94) cited by Levene et al (1970) seem unrealistic considering that the long term repeatability of applanation pressures does not exceed 0 8 (The heritability is defined as the ratio of additive genetic variance to phenotypic variance The repeatability expresses the proportion of the variance of single measurements that is due to permanent differences between individuals – both genetic and environmental The figure given here has been

calculated from a distribution of differences in tension between two visits five to seven years apart reported by Perkins 1973) According to this view the general level of resemblance between relatives and spouses changed little from Iowa and New York to Dalby – in spite of possible differences in environment age and degree of heterogeneity of the populations

If spouses are omitted the observed resemblances between relatives were more marked in USA than in Sweden The total variance of the intraocular pressure was also greater in USA – particularly in New York Such data lend support to an assumption that the Swedish population is more genetically homogeneous which might offer a partial explanation of our observations indicating that environment is relatively more important in Sweden than in USA

The results of our efforts to obtain information concerning the nature of a possible common environment were not gratifying The increase in resemblance between relatives with age might be interpreted as being cau ed by slowly accumulative effects Food and drinking habits acquired during adolescence and maintained after leaving home seem to be the most obvious possibility since characters connected with metabolic processes e g secretion are often susceptible to nutritional factors

The present study has dealt with the variability of ocular pressure in normal eyes It provides no basis for speculations concerning the relative importance of inheritance and environment in glaucoma *Generally speaking characters* more important as determinants of natural fitness exhibit less genetic variation The explanation usually given is that natural selection strongly favours the optimal genotype On the other hand deviations from a more or less ubiquitous genotype can be expected to affect fitness Our suspicion that the heritability of intraocular pressure in normal eyes may be low is therefore by no means incompatible with the opinion that most of the primary glaucomas are genetically determined diseases The possible role of environment in the causation of simplex glaucoma remains to be explored

Acknowledgement

I wish to express my thanks to professor Marianne Rasmussen Umeå for valuable criticism

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THE KNAPP RØNNE TYPE OF MALIGNANT MELANOMA OF THE CHOROID

A haemangioma like melanoma with a typical clinical picture
So called preretinal malignant choroidal melanoma

BY

O A JENSEN

Five cases of a rare type of malignant melanoma of the choroid with a typical clinical and histopathological picture are reported This tumour is characterized by its location near the optic disk its early growth through the retina its structure with bloodless and blood filled cavernous spaces and its manifestation by a massive haemorrhage into the vitreous Historical cases are mentioned showing that this rare tumour occurring in about 1 250 of malignant melanomas of the choroid has a Scandinavian tradition The clinical and histopathological details are discussed

About 10 years ago I called attention to a type of malignant melanoma of the choroid with a typical clinical and histopathological picture (Jensen 1964)

The German ophthalmologist H Knapp was the first to mention this type of tumour in 1868 Later typical cases were described by the Danish ophthalmologist C V Lodberg (1913) (Fig 1) and F Berg of Sweden (1914) (Figs 2 3) H Ronne the late professor of ophthalmology in Copenhagen compiled the previously published cases and himself added a new case (1923 1929 1936) (Fig 4) In some respects therefore it is a tumour with a Scandinavian tradition

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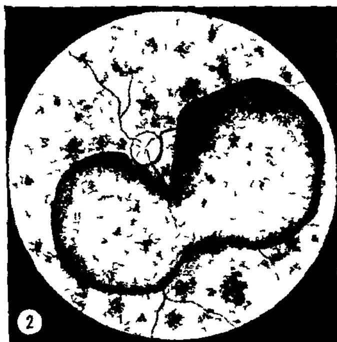
Fig 1
The remnants of the original tumour seen by Lodberg The arrows indicate the area where the retina is perforated Celloidin embedding Van Gieson Lab No 61/11 (×25)

Similar cases were later published by Gass (1963) and Wolter et al (1973)
Since I have now collected four additional cases it may be appropriate once again to refer to this type of tumour particularly as we can now reveal the tumour by means of ultrasound in spite of its most typical clinical manifestation the vitreous haemorrhage which impedes ophthalmoscopy

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Fig 2
Drawing in the publication by Berg (his Fig 1) showing the tumour near the optic disk and the retinal vessels disappearing behind the tumour Reproduced from Klin Mbl Augenheilk 53 116 (1914) by courtesy of the editor

Fig 3
Drawing in the publication by Berg (his Fig 2) showing a section with masses of spongy tumour tissue in the vitreous cavity Reproduced from Klin Mbl Augenheilk 53 118 (1914) by courtesy of the editor


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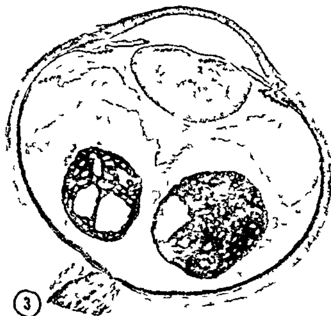

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Fig 1
The remnants of the original tumour seen by Lodberg The arrows indicate the area where the retina is perforated Celloidin embedding Van Gieson *Lab No 61/11 (× 25)*

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Drawing in the publication by Berg (his Fig 2) showing a section with masses of spongy tumour tissue in the vitreous cavity Reproduced from Klin Mbl Augenheilk 53 118 (1914) by courtesy of the editor

Table I
Summary of clinical data

Case No	Rec No	Sex	Age	Side	Past history	Presenting symptoms	Vision at examination	Sign	Alive after	Dead after	Cause of death
1	975/68	F	55	R	1 year	Sudden loss of vision	1/60	White tumour with haemorrhages	12 years	–	–
2	197/69	F	71	L	2 months	Sudden brown red mist	1/60	Choroidal haemorrhages	6 years	–	–
3	27/70	M	82	L	Unknown	Loss of vision	No light perception	Glaucoma Fundus not visible	–	1 month	Cerebral haemorrhage
4	841/70	M	57	L	3 weeks	Black shadow	Perception of light	Black tumour with large haemorrhages	–	2 years	Metastases
5	715/71	F	76	L	6 months	Black shadow	6/18	No retina on tumour Small vitreous haemorrhages	4 years	–	–

Table II
Summary of histopathology

Case No	Rec No	Localization	Shape	Pigment	Scleral invas
1	275/63	Near disk	M	+	–
2	197/69	Near disk	M	+	–
3	27/70	On disk	M	(+)	–
4	841/70	On disk	M	+	–
5	715/71	Postero temp	M	(+)	–





Fig 5
Sectioned eyeball showing a mushroom shaped tumour with spongy structure and a large vitreous haemorrhage Case No 2 Lab No 197/69 (× 2 5)

Fig 6
Histopathological section of the same tumour as in Fig 5 It can be seen that the haemorrhage has been washed out *during preparation* Case No 2 *Haematoxylin eosin* Lab No 197/69 (× 3)

Table II (cont)

ruch/retina	Cell type	Necroses	Vascular lumina	Cavernous spaces	Vitreal haem	Size mm³
P	Small epith	–	+++	+++	+	720
P	Mixed	–	+++	++	+	500
P	Epith	–	++	+++	+	510
P	Epith	–	++	+++	+++	2 00
P	Mixed	–	+++	+	+	1000

Abbreviations M = mushroom – → +++ = degree of parameter P = perforated

Pathology

All enucleated eyeballs were formalin fixed and processed routinely They were stained with haematoxylin eosin and van Gieson The most important histopathological findings are shown in Table II It is noticed that all tumours were located near the disk

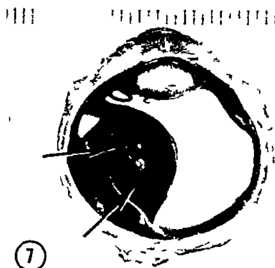


Fig 7
Sectioned eyeball demonstrating that the tumour head has perforated the retina. Arrows indicate the site of perforation. Case No 5 Lab No /15/71 (x 9 5)

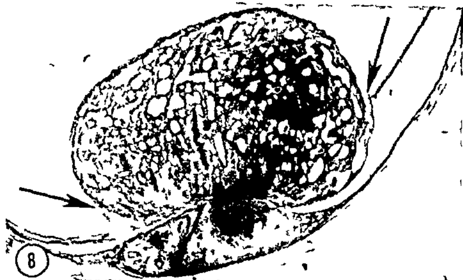




Fig 8

The typical spongy structure of the head and solid structure of the base Arrows indicate where the retina is perforated Case No 1 Haematoxylin eosin Lab No 275/63 (× 8)

Fig 9

Another typical tumour with both vascular and bloodless spaces Note the many spaces near the vitreous cavity Arrows indicate where the retina is perforated Case No ? Haematoxylin eosin Lab No 197/69 (× 10)

Fig 10

Vascular lumen lined with endothelial cells The tumour cells are round with large vascular nuclei with distinct nucleoli and abundant cytoplasm (Epithelioid cell type) Case No 1 Haematoxylin eosin Lab No 275/63 (× 550)

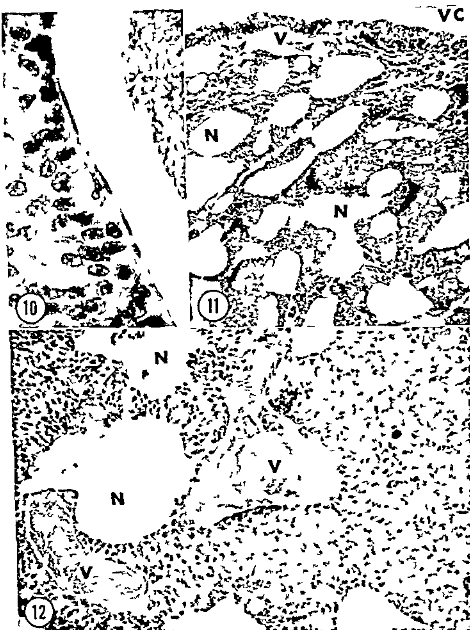
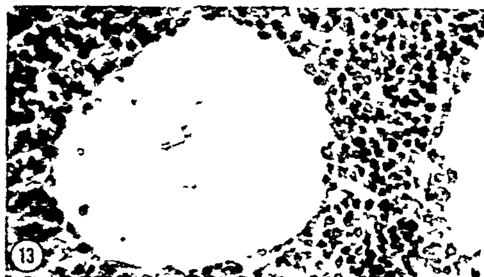


Fig 11
Numerous vascular (V) and non vascular (N) spaces lying close to the vitreous cavity (VC) Case No 1 Haematoxylin eosin Lab No 275/63 (× 95)

Fig 12
Vascular spaces (V) lying close to bloodless spaces (N) Case No 1 Haematoxylin eosin Lab No 275/63 (× 100)


13


14


V
15

(without invading it) (Figs 5 6) and that extension through Bruch s membrane (giving the mushroom – or fungiform – shape) as well as through the retina had occurred in all cases (Figs , 8 9) The tumour cells were somewhat anaplastic with cell types from mixed to epithelioid (Fig 10) (Callender s classification) and all tumours were only slightly pigmented. A common feature was large vascular spaces (Figs 9 10 12) and cavernous spaces without blood giving a spongy structure (Figs 8 9 11) Looking at Fig 1? it appears that vessels lying close to the bloodless spaces may easily rupture into these In some of the bloodless spaces the lining is definitely of tumour cells (Fig 13) but in others or in certain parts of some either a flattening of tumour cells towards the lumen or the ingrowth of endothelium from ruptured vessels appears to have taken place (Fig 14) Due to washing out during preparation only remnants of vitreal haemorrhage clinically so conspicuous were found in the sections (Fig 6) No inflammatory signs necrosis or remnants of necrosis such as scar tissue were observed

Comment

The melanoma concerned is a rarity Between 1945 and 19/4 we have listed 1230 malignant melanomas in our files Only the present five cases belong to the Knapp Rønne type The tumour is characterized by its location and structure leading to a typical clinical manifestation The extension through Bruch s membrane causing the mushroom fungiform or collar button shape is well known The tumour breaks through the retina probably because of its location near the optic disk where the retina is tightly bound to the underlying structures so that it has no possibility of retreating before the expanding tumour Another factor may be the aggressiveness of the tumour tissue reflected in the anaplas ic cells However not all malignant melanomas located near the disk break through the retina and in my experience particularly not the more differentiated As the less differentiated tumours grow faster than the more dif

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Fig 13
Bloodless space lined tumour cells Filamentous material in the centre Case No 3 Haematoxylin eosin Lab No 27/ 0 (×2/5)

Fig 14
Space lined with tumour cells and flat endothelium like cells (arrows) Case No 1 Van Gieson Lab No 275/63 (×275)

Fig 15
Compression of tumour tissue and vessels at the site where Bruch s membrane is penetrated (arrow) V dilated vessels Case No 5 Van Gieson Lab No 15/71 (×25)

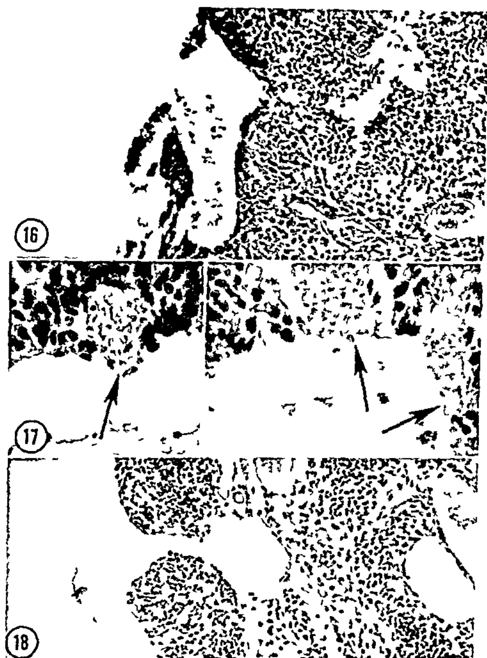


Fig 16

Vascular space rupturing into the vitreous cavity Case No 2 Haematoxylin eosin Lab No 197/69 (× 100)

ferentiated the speed of growth may be of importance Mitoses however were no more frequent in these tumours than in ordinary mixed or epithelioid cell types (which incidentally have more mitoses than the spindle cell types) As concerns the two kinds of space in the tumour the production of the *vascular* spaces is due to strangulation of vessels where the tumour grows through Bruch s membrane (Fig 15) These dilated vascular lumina may be ophthalmoscopically demonstrated by fluorescein injection as a worm like configuration on the naked tumour surface (Wolter et al 19/3) It is not surprising that vitreous haemorrhage is a constant feature in the clinical picture (Fig 16)

Cavernous spaces without blood (Figs 11 14) are much more difficult to explain Berg (1914) was already highly interested in these which he called cysts He said that blood was never found within them but that they contained a coagulated solution He also noticed that the lining of the lumen was mostly tumour cells but that sometimes a layer of flat endothelium like cells was observed He never observed connections between the blood filled and the bloodless spaces In the present cases I have found in these spaces a few erythrocytes and definitely ruptured vessels (Fig 17) which suggests that endothelium might have grown from primarily vascular spaces into primarily bloodless spaces and so to say transformed these into vascular spaces

How these primarily bloodless spaces arise is still obscure They are *not* formed on a basis of necrosis as this has never been met in these tumours (including the previously published cases) The characteristic accumulation of melanophages in and around necrotic areas as is seen in usual melanomas was not observed in any of these tumours Ronne (1923) was convinced that a relationship existed between the retinal perforation and the formation of caverns This may be true Thus it may be hypothesized that the rapid contact with the vitreous gives excellent conditions for growth so that columns of tumour cells shoot into the vitreous and in some way encircle small parts of it forming cysts (Fig 18) Some of these may then be vascularized secondarily if vessels rupture into them whereas others remain bloodless The fact that

Fig 17

Vessels rupturing into bloodless spaces (arrows) Filamentous material in the center Case No 1 Haematoxylin eosin Lab No 2/5/63 (x 2/5)

Fig 18

Processes of tumour tissue rich in cells They are apparently encircl rg a part of the vitreous cavity When they reach each other a bloodless space has been formed Case No 1 Haematoxylin eosin Lab No 2/5/63 (x 100)

the scanty filamentous material found in some bloodless cavernous spaces is positively stained by Alcian blue with 1 M MgCl and negatively after digestion with testicular hyaluronidase supports this hypothesis

Rønne (1923 1929 1936) called attention to an interesting clinical feature He found a scotoma corresponding strictly to the size of the tumour and not the expected visual field defect peripheral to the tumour due to nerve fiber destruction Rønne therefore concluded that the fibers were not destroyed but only pushed aside Unfortunately careful examination of the visual fields was not performed in the present cases

As a point of interest it may be mentioned that Rønne was contemptuous of the paradoxical term *preretinal choroidal* melanoma

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CHORIO RETINAL RESECTION OF A NEOPLASM FROM THE HUMAN EYE

BY

PEEP ALGVERE and ERIK KOCK

An epithelioma was removed from the iris and ciliary body of a six year old girl by a partial irido cyclectomy Three months later recurrence of the tumour was seen in the equatorial zone of the fundus
Three weeks after application of transscleral cryotherapy around the neo plasm a chorio retinal resection of the tumour area in the fundus was performed
The postoperative healing was satisfactory Re examination 16 months later revealed a healthy eye
The results indicate that a circumscribed tumour can successfully be re sected from the fundus

Key words chorio retinal resection – human eye – epithelioma of the ciliary body – electron microscopy – modified Flieringa s ring

This paper concerns a young girl with a neoplasm of the iris and ciliary body with growth posteriorly into the choroid as far as the equatorial zone of the fundus The tumour was successfully removed by a chorio retinal resection

Case history

A six year old girl consulted an ophthalmologist for increasing conjunctival injection *in her left* eye a symptom which first appeared in May 1973 She was treated with eye drops for conjunctivitis In August a pink coloured tumour with many dilated vessels was seen in the chamber angle The tumour measured 1 5 x 5 mm and on transpupillary

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illumination there was a shadow over the upper nasal quadrant of the eye reaching almost as far as the equatorial region

Since the visual acuity was normal the eye was at first observed without further measures However a steady growth was noted and in November 1973 the anterior part of the tumour extended half way between the chamber angle and the pupillary margin (Fig 1) The periphery of the fundus was normal A partial cyclectomy was performed but the surgeon observed tumour material in the periphery The histo pathological examination confirmed that the tumour had not been completely resected Visual acuity was 5/7 5 When examined in January 1974 no local recurrence was observed

Three months later a gray mass was visible in the peripheral fundus confluent with the pars plana ciliaris Further growth was noted and in May 1974 the tumour was seen at the equatorial region of the fundus (Fig 2) The visual acuity of the left eye had gradually deteriorated to finger counting at 3 m It was known from the histo pathological examination of the previously resected part of the tumour that this neoplasm was of an infiltrative nature (see microscopic examination) Due to the rapid progression of the neoplasm a resection was made by one of us (P A)

Surgical procedure

To prevent detachment of the retina cryotherapy was applied around the neo plasm through full sclera beneath a conjunctival flap This was done under ophthalmoscopical control Three weeks later the tumour was resected in the following manner

The conjunctiva was incised traction sutures were placed under the superior and medial rectus muscles The tumour was localized and its shape marked on the sclera A modified Flieringa s ring with a semicircular appendix was firmly attached to the sclera with silk sutures (Fig 3) The sclera was incised a few mm from the limbus and a full thickness scleral flap (about 5 mm wide) was dissected as far as the equatorial region of the eye The tumour was not adherent to the sclera and was easily exposed Rows of diathermy burns were applied around the tumour to prevent bleeding The neoplasm was resected with Vannas scissors by cutting the underlying choroid and retina These were then cautiously removed from the vitreous surface There was some vitreous prolapse and a vitrectomy ab externo was performed with the scissors The sclera was closed with a tight row of 8-0 silk sutures and covered by the conjunctival flap

The postoperative healing was satisfactory and the inflammatory reaction caused by surgery subsided in a few weeks The eye was reexamined every 2-4 months To date (September 1975) the patient has been observed for 16 months postoperatively The eye shows no inflammatory reaction The lens and vitreous are clear The fundus is easily seen and reveals the resected area with bare sclera surrounded by pigmented scar tissue of the retina and choroid There is no detachment of the retina (Fig 4) Visual acuity is 0 1 corresponding to 0 9 (with stenopaeic hole) There is no corneal astigmatism (Javal is spherical)



Fig 1
Photograph of the anterior segment of the eye shows tumour growth on the iris as seen through the cornea The tumour was pink coloured and richly vascularized Above it, there are some dilated episcleral vessels (November 1973)



Fig 2
Fundus photograph of the choroidal part of the tumour situated in the upper nasal quadrant of the fundus and reaching the equatorial zone of the eye (May 1974)



Fig 4
Fundus photograph 6 months after resection of the tumour The border of the chorio retinal resection is seen as a pigmented zone above which the whitish sclera is visible. The supero nasal vortex vein ampulla is distinguishable to the right

Histo pathological Examination

Macroscopic examination

I The specimen from the first operation consisted of a 10 x 4 mm large gray solid tumour tissue which appeared to be totally extirpated except posteriorly

II The specimen from the second operation was 8 x 5 x 4 mm had the same colour and consistency as the first tumour and appeared to be totally extirpated

Microscopic examination

I The specimen from the first operation The tumour is composed of slightly *polymorph epitheloid cells with granular cytoplasm The central and posterior* parts of the tumour are hyalinized Only a few mitoses are seen Between the tumour cells there are some pigmented melanocytes but the tumour cells them selves are not pigmented The reticulin is quite well developed No myofibrils are observed in the sections stained with PTAH or Masson s trichrome The tumour is totally extirpated except posteriorly

II The specimen from the second operation The tumour which had now been *totally extirpated has the same appearance as described in the first specimen* However the tumour is now more cellular and without degenerative changes

III Ultrastructure examinations of both specimens do not show any diagnostic elements such as myofibrils or pigment granules This seems to rule out myogenic and melanogenic tumours

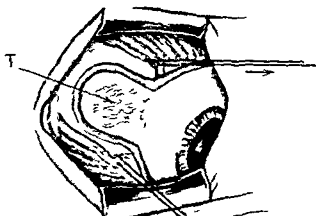


Fig ɔ

Schematic drawing of the eye at operation A modified Flieringa s ring is sutured to the sel ra just anteriorly to the insertions of the rectus muscles The appendicular part of *the ring surrounds the tumour area* (T depicted as dark area)

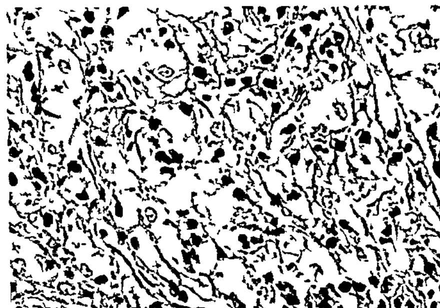


Fig 5

Micrograph of the neoplasm classified as an epithelioma originating from the ciliary body The tumour cells have polymorphous nuclei and are not pigmented Between the tumour cells there are some pigmented melanocytes The reticel is quite well developed Hematoxyline eosin (x 500)

It is difficult to make an exact histo pathological diagnosis of this tumour The most likely diagnosis seems to be an epithelioma of the ciliary body The tumour shows an infiltrative growth but the cytology does not give the impression of general malignancy (Fig 5)

Discussion

A partial iridocyclectomy (Stallard 1973) is an appropriate surgical procedure for removing a neoplasm from the iris and ciliary body The resection of a neoplasm in the choroid which often affects the retina has generally been considered impossible However an experimental approach to a full thickness eye wall resection was taken by Peyman et al 1972a b 1974) These authors reported satisfactory healing of rabbit eyes that had undergone a full thickness resection of the sclera choroid and retina

When tumour growth into the scleral lamellae is expected a sclerectomy is certainly necessary and the resected area should be covered by a graft of scleral

or corneal tissue In the case presented a previous microscopic examination had shown that the sclera was not affected Under these conditions a chorio retinal resection seems to be justified

When operating in the choroid deleterious complications easily occur The major hazards are probably uveal hemorrhage and retinal detachment To avoid the former careful diathermy of the vascularized tissue must be carried out around the area to be resected The risks for retinal detachment are minimized by previous cryo or diathermy treatment which when applied a few weeks before the resection produces firm chorio retinal scars

In the case presented some vitreous loss occurred The prolapsing vitreous was cut ab externo by scissors A vitreous haze was observed during the first post operative week most probably due to a slight hemorrhage These complications subsided rapidly and the eye healed satisfactorily

This favourable healing shows that a partial chorio retinal resection of a limited area can successfully be performed and that a neoplasm can thus be removed from the human eye In the future a local resection of a circumscribed tumour of the fundus should always be considered as long as the pathological changes remain localized to an area that is surgically easily accessible i e preferably in the anterior part of the fundus This treatment is especially suited for neoplasms which show an infiltrative local growth but with little or no tendency towards general malignancy

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PROGNOSIS OF PRIMARY RHEGMATOGENOUS RETINAL DETACHMENTS

2 Accounting for and predicting final visual acuity in surgically reattached cases

BY

PAUL L KAUFMAN

Multiple linear regression analysis of variance was used to define relationships between final visual acuity and several parameters in 31 patients with reattached primary rhegmatogenous retinal detachments Older patient age preoperative macular detachment clinically visible macular lesions greater detachment duration and extent and higher subretinal fluid butyrylcholinesterase activity were all inversely related to final acuity The relationship of each parameter to final acuity in conjunction with and apart from all the other parameters was defined Collectively the parameters accounted for 85% of the variation about the mean of the clinically observed finally acuities The parameters could be weighted to give a generally reasonably accurate prediction of final acuity at the time of surgery The findings are consistent with a pathophysiological sequence involving alterations in the choroidal circulation and the blood ocular barrier of the posterior segment

Key words butyrylcholinesterase – macula – retina – retinal detachment – subretinal fluid

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The parameters which determine the final visual acuity in reattached primary rhegmatogenous retinal detachments (PRRD) are not well defined. The conventional methods of evaluating the importance of a suspected parameter are to compare the visual outcome of patients who differ with respect to that parameter, compare the magnitude or prevalence of the parameter among patients with different visual outcomes, or correlate the parameter with visual outcome (Jay 1965, Gundry & Davies 1974, Kaufman 1975). These approaches ideally require either that the different patient groups be matched with respect to all other important parameters or that these other parameters be randomly distributed with respect to the parameter and the patients under study. Such conditions can hardly be met, since so few important parameters are known, and even those are interrelated (Kaufman & Podos 1973a, Kaufman 1975).

This communication will show that multiple linear regression (MLR) analysis of variance (ANOVA) techniques applied to a small patient series permit evaluation of parameters suspected of influencing visual outcome in surgically reattached PRRD, and that final visual acuity in these patients could be largely accounted for and predicted from a handful of parameters.

Material and Methods

Thirty one eyes of 31 patients underwent scleral buckling procedures with drainage of subretinal fluid (SRF) to repair their PRRDs. Each retina was reattached and each eye was followed for at least six months (mean = 12.5 months) after surgery. Each eye was without severe vitreal or retinal pathology and each had a clear cornea and vitreous and, if phakic, no more than minimal lens changes. Other criteria for inclusion in the study, the definition and determination of the clinical detachment characteristics and final visual acuity, basic demographic information, the therapy employed, the methods for obtaining SRF and plasma and assaying their butyrylcholinesterase (BuChE) activity, the type of clinical follow up and the conventional statistical analysis of the raw data have been previously described (Kaufman & Podos 1973a, Kaufman 1975).

MLR ANOVA on the raw data, using standard (Draper & Smith 1966, Wonnacott & Wonnacott 1969) commercially computerized (Hewlett Packard Co.) methodology provides:

1. A regression equation describing final acuity (Y) as a function of all parameters (X's). For k parameters this takes the form

$$Y_i = b_0 + b_1 X_{i1} + \dots + b_k X_{ik} + E_i \qquad i = 1, 2, \dots n$$

where it is assumed that E_i are independent and normally distributed with mean = 0 and variance unknown.

2 An F ratio for the regression (F regression) from which the significance of the regression may be evaluated

3 An F ratio ($F_{\backslash p}$) for the regression coefficient of each parameter indicating whether the coefficient (the b values in the regression equation) differs significantly from 0 that is whether final acuity is related to that parameter

4 A coefficient of determination (R the proportion of the total variation of the acuities about the mean which is explained by fitting the regression)

5 A correlation coefficient (R) between the observed final acuities and the final acuities calculated from the regression equation

The parameters considered were

A Patient age (mean ± SD = 60 4 ± 18 3 years range = 14–88 years)

B Log_{10} detachment duration (mean ± SD = 32 8 ± 66 0 days range = 4–365 days geometric mean = 15 0 days SD = 0 483 log units (i e coefficient of variation = 204 %))

C Detachment extent (mean ± SD = / 5 ± 2 8 clock hours range = 2 5–12 clock hours)

D SRF BuChE activity (mean ± SD = 4 24 ± 4 26 % of plasma enzyme activity range = 0 00–18 87 % of plasma activity)

Macular parameters and phakic/aphakic status were treated as categorical (on off) variables (Wonnacott & Wonnacott 1969)

E Macular detachment if the macula had been detached preoperatively a value of 1 was assigned if it had not been detached 0 was used (24 detached 7 not detached

F Macular pathology if a macular lesion was present a value of 1 was assigned if no lesion was present 0 was used Nine eyes demonstrated macular lesions postoperatively fibroplasia (4) pigment fallout from cryotherapy (2) cyst (2) demarcation line (1) In one eye with fibroplasia and one with a cyst the lesion was present at surgery but presumably not prior to the detachment

G Phakic aphakic status if the patient was aphakic a value of 1 was assigned if he was phakic 0 was used (14 aphakic 1/ phakic) No eye was made aphakic during the study

H Duration of follow up after surgery (mean ± SD = 12 5 ± 4 0 months range = 6–20 months)

Y Final visual acuity the decimal equivalent of the Snellen fraction was used (mean ± SD = 0 319 ± 0 218 range = 0 009–0 66) In three patients acuity

had been recorded as counting fingers at a distance d cm This was converted to an approximate decimal acuity as follows the width of a finger and the distance between fingers were each taken as 2 cm If the patient s minimum visual resolution angle was O (minutes) then Tan $(\Theta/2) = 1/d$ $O/2$ was determined from trignometric tables and O calculated A Snellen acuity of 20/20 equivalent to a decimal acuity of 1 0 demands a resolution angle of one minute and the patient s decimal acuity $\approx 1/O$

The sequence in which the parameters are considered in ANOVA can influence the F_{X_p} s (Draper & Smith 1966) Therefore for each parameter X_p

1 X_p will be considered first in the ANOVA F_{X_p} will thus be determined on the basis of all the information about final acuity carried by X_p regardless of whether other parameters also carry this information

2 X_p will be considered last in the ANOVA F_{X_p} will thus be determined on the basis of the unique information X_p carries about final acuity that is information not carried by the other parameters

3 The parameters will be sequenced to give the maximum possible F_{X_p} – i e to show the strongest possible relationship between X_p and final acuity If F_{X_1} is strongly significant by both 1 and 2 however this operation contributes little and will be omitted

4 X_p will be deleted from the model The decrease in R^2 will then reflect the unique information X_p carries about final acuity

Results

The MLR ANOVA findings are presented as follows Tables I and II show the results of the various ANOVAs Pertinent regression equations each numbered according to one of its corresponding ANOVAs are shown in Table III Each panel of Fig 1 plots the final acuity observed clinically for each case against the acuity calculated from one of the regression equations of Table III each panel is numbered according to its corresponding regression equation and ANOVA

Accounting for final acuity (Table I) With all the parameters and all 31 cases included MLR gives Equation 1 Table III More than four fifths of the variation about the mean in the observed final acuities was explained by fitting this regression ($R = 0\ 817$) making the regression highly significant (F regression = 12 26 $P < 0\ 001$ ANOVA 1 Table I A)

The agreement between the clinically observed acuities and the calculated ones was generally quite good with R = 0 904 (Fig 1 panel 1)

Length of follow up and phakic/aphakic status carried very little information about final acuity the F ratios for their regression coefficients were nonsignificant regardless of the positions these parameters occupied in the ANOVA and R and R were virtually unchanged when both parameters were deleted (compare ANOVAs 1 and 2 in Table IA with respect to R and R) Therefore these two parameters were not considered in any subsequent ANOVAs and equations

Patients age (ANOVAs 2–4) macular detachment (ANOVAs 3 to 6) and macular pathology (ANOVAs 5 to 8) each carried significant unique information about final acuity (i e the F ratios of their regression coefficients were significant when the parameter was considered last in the analysis) Each carried additional information which was not unique patient age shared information with detachment extent and macular detachment macular detachment shared information with patient age and macular pathology macular pathology shared information with macular detachment (these relationships are reflected by the changes in the F_{X_n}s as the parameter sequence is varied or parameters are deleted) Deleting both macular parameters caused the loss of nearly half the information about final acuity (ANOVA 9)

Detachment duration (ANOVAs 7 11 12) detachment extent (ANOVAs 11 13 14) and SRF BuChE (ANOVAs 15 16 17 2) each carried significant information about final acuity but most of the information carried by each was also carried by other parameters Deleting any one of these three parameters caused only a minimal loss of information (ANOVAs 12 14 17) but deleting all three caused considerable loss (ANOVA 18) Restoring either detachment duration (ANOVA 19) or detachment extent (ANOVA 20) restored about half this lost information but restoring only SRF BuChE returned nearly all of it (ANOVA 21) Thus SRF BuChE carried essentially the same information about final acuity as did detachment duration and extent collectively

Final acuity could be accounted for reasonably well using all six significant parameters (ANOVA Eq Panel 2) or the five clinical parameters (ANOVA Eq Panel 17) or patient age the two macular parameters and SRF BuChE (ANOVA Eq Panel 21)

The 31 cases were then divided into three groups according to macular status no macular detachment and no visible macular pathology (7 cases) macular detachment but no macular pathology (15 cases) macular detachment and a visible macular lesion (9 cases) Each group was analyzed separately For the 7 cases without macular detachment or pathology (Table IB) a statistically significant relationship between final acuity and any of the remaining para

had been recorded as counting fingers at a distance d cm This was converted to an approximate decimal acuity as follows the width of a finger and the distance between fingers were each taken as 2 cm If the patient s minimum visual resolution angle was Θ (minutes) then $\text{Tan } (\Theta/2) = 1/d$ $\Theta/2$ was determined from trignometric tables and Θ calculated A Snellen acuity of 20/20 equivalent to a decimal acuity of 1 0 demands a resolution angle of one minute and the patient s decimal acuity $= 1/\Theta$

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Results

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Accounting for final acuity (Table I) With all the parameters and all 31 cases included MLR gives Equation 1 Table III More than four fifths of the variation about the mean in the observed final acuities was explained by fitting this regression ($R = 0.817$) making the regression highly significant (F regression = 12 26 $P < 0.001$ ANOVA 1 Table I A)

The agreement between the clinically observed acuities and the calculated ones was generally quite good with R = 0 904 (Fig 1 panel 1)

Length of follow up and phakic/aphakic status carried very little information about final acuity the F ratios for their regression coefficients were nonsignificant regardless of the positions these parameters occupied in the ANOVA and R and R were virtually unchanged when both parameters were deleted (compare ANOVAs 1 and 2 in Table IA with respect to R and R) Therefore these two parameters were not considered in any subsequent ANOVAs and equations

Patients age (ANOVAs 2–4) macular detachment (ANOVAs 3 5 6) and macular pathology (ANOVAs 5 7 8) each carried significant unique information about final acuity (i e the F ratios of their regression coefficients were significant when the parameter was considered last in the analysis) Each carried additional information which was not unique patient age shared information with detachment extent and macular detachment macular detachment shared information with patient age and macular pathology macular pathology shared information with macular detachment (these relationships are reflected by the changes in the F_{Xp} s as the parameter sequence is varied or parameters are deleted) Deleting both macular parameters caused the loss of nearly half the information about final acuity (ANOVA 9)

Detachment duration (ANOVAs 7 11 12) detachment extent (ANOVAs 11 13 14) and SRF BuChE (ANOVAs 15 16 17 2) each carried significant information about final acuity but most of the information carried by each was also carried by other parameters Deleting any one of these three parameters caused only a minimal loss of information (ANOVAs 12 14 17) but deleting all three caused considerable loss (ANOVA 18) Restoring either detachment duration (ANOVA 19) or detachment extent (ANOVA 20) restored about half this lost information but restoring only SRF BuChE returned nearly all of it (ANOVA 21) Thus SRF BuChE carried essentially the same information about final acuity as did detachment duration and extent collectively

Final acuity could be accounted for reasonably well using all six significant parameters (ANOVA Eq Panel 2) or the five clinical parameters (ANOVA Eq Panel 17) or patient age the two macular parameters and SRF BuChE (ANOVA Eq Panel 21)

The 31 cases were then divided into three groups according to macular status no macular detachment and no visible macular pathology (7 cases) macular detachment but no macular pathology (15 cases) macular detachment and a visible macular lesion (9 cases) Each group was analyzed separately For the 7 cases without macular detachment or pathology (Table IB) a statistically significant relationship between final acuity and any of the remaining para

Table 1

ANOVA Accounting for final acuity in surgically reattached PRRD

ANOVA No.	Parameter sequence	F regression	R	R	F_A (patient age)	F_B (detachment duration)	F_C (detachment extent)	F_D (SRF Hb(Hb))	F_E (macular detachment)	F_F (macular pathology)
					A All cases (n = 31)					
1*	X	12.2(b)	0.817	0.901(b)	X	X	X	X	X	X
2	AEFBCD	16.4(b)	0.804	0.897(b)	86.8(b)	13.2(b)	8.1(b)	2.07(a)	91.35(b)	4.59(b)
3	EFBCDA	16.4(b)	0.804	0.897(b)	3.80(b)	9.01(b)	15.76(b)	4.8(b)	39.57(b)	4.29(a)
4	EFBCD	[illegible]	0.737	0.860(b)		7.58(b)	17.80(b)	4.07(a)	49.4(b)	9.5(a)
	FBCDAE	16.46(b)	0.804	0.897(b)	19.11(b)	9.31(c)	27.57(b)	3.6(a)	17.72(b)	21.19(b)
6	FBCDA	[illegible]	0.660	0.812(b)	11.4(c)	5.5(b)	16.67(b)	2.90		19.66(c)
7	BCDAEF	16.46(b)	0.804	0.897(b)	34.0(b)	17.1(b)	4.6(b)	2.37	31.92(b)	10.37(c)
8	BCDAE	12.8(b)	[illegible]	0.849(b)	17.96(b)	3.4(a)	17.93(b)	1.72	23.72(b)	
9	BCDA	[illegible]	0.460	0.678(b)	9.68(b)	1.86	9.67(c)	0.98		
10	FABCDE	16.46(b)	0.804	0.897(b)	31.60(b)	16.07(b)	10.70(b)	1.58	17.72(b)	21.19(b)
11	CDAEFB	16.46(b)	0.804	0.897(b)	31.91(b)	2.67	28.27(b)	3.13(a)	38.14(b)	9.38(b)
12	DCAEF	18.06(b)	0.789	0.885(b)	30.58(b)		10.09(c)	19.75(b)	31.12(b)	8.81(c)
13	FBDAEC	16.16(b)	0.804	0.897(b)	27.28(b)	9.31(c)	2.18	20.37(b)	19.99(b)	21.19(b)
14	DBAEF	18.01(b)	0.789	0.885(b)	23.78(b)	0.00		19.60(b)	39.05(b)	9.00(b)
15	DBCAEF	16.46(b)	0.804	0.897(b)	31.0(b)	0.00	10.39(c)	21.07(b)	31.92(b)	10.37(c)
16	EFDBCA	16.4(b)	0.804	0.897(b)	3.80(b)	0.58	4.20(b)	24.9(b)	39.57(b)	4.29(a)
17	BCAEF	17.76(b)	0.780	0.883(b)	21.1(d)	4.90(b)	22.86(b)		27.84(b)	9.93(b)
18	AEF	18.0(b)	0.604	0.777(b)	20.45(b)				17.95(b)	2.71
19	AEFB	16.05(b)	0.712	0.844(b)	27.08(b)	0.77(b)			24.76(b)	3.59(a)
20	AEFC	16.60(b)	0.719	0.848(b)	27.71(b)		10.63(c)		24.94(b)	3.78(a)
21	AEFD	[illegible]	0.703	0.838(b)	32.18(b)			1.45(b)	29.03(b)	4.37(b)

				B *Cases without macular detachment or macular path logy (n =)*				
22	ABCD	0.36	0.471	0.647	0.38	0.50	0.05	0.52
23	ADBC	0.36	0.491	0.647	0.38	0.12	0.49	0.46
				C *Cases with macular detachment but without macular pathology (n = 1)*				
24	ABCD	7.17[b]	0.749	0.861[d]	19.46[d]	3.18)	3.71)	2.34
25	ADBC	7.17[b]	0.749	0.861[d]	19.46[d]	0.51	0.89	7.82[b]
26	ABC	7.83)	0.681	0.895[d]	17.35)	2.84	3.31[a]	
27	AD	14.35)	0.705	0.840[d]	20.47[d]			8.93[d]
28	A	13.16[c]	0.503	0.709)	13.16)			
				D *Cases with macular detachment and macular pathology (n = 9)*				
29	ABCD	14.92[b]	0.937	0.968[d]	0.22	35.78[d]	19.84[c]	3.86)
30	ADBC	14.92[b]	0.937	0.968[d]	0.22	7.74[b]	23.49)	28.99)
31	ABC	11.84[b]	0.877	0.936[d]	0.14	22.76)	19.62)	
32	AD	2.48	0.448	0.669[b]	0.04			4.89)
33	ABD	2.91	0.570	0.755[d]	0.39	6.58[b]		0.52
34	ACD	24.66)	0.937	0.968[d]	0.27		67.89	5.83[b]

A blank F_{X_i} means that parameter was not considered in that ANOVA

Includes the six listed parameters plus Follow up Duration and Phakia/Aphakia F_{X_p}s not shown
Follow up Duration and Phakia/Aphakia not considered in subsequent ANOVAs
Significance of F regression R and F_{X_r} (2 tailed tests)) $P < 0.10$ b) $P < 0.05$) $P < 0.01$ d) $P < 0.001$

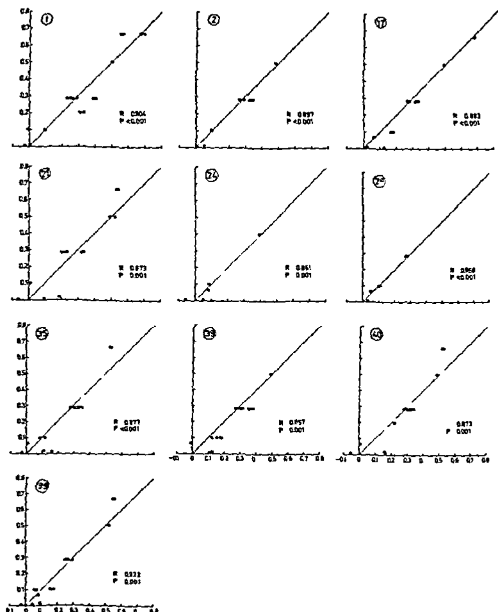


Fig 1

Calculated final visual acuity (abscissa) vs clinically observed final visual acuity (ordinate) Circled number on each panel represents the number of the equation in Table III from which the calculated acuities in that panel were determined (except for panel 99 for which the equation is not given) The 45 degree line in each panel represents identity between observed and calculated acuities R is the coefficient of correlation between observed and calculated acuities

Table II

ANOVA Predicting final acuity in surgically reattached PRPD

ANOVA No	Parameter sequence	Γ regression	R	R	F_A (patient age)	F_B (detachment duration)	F_C (detachment extent)	F_D (SRF BuChF)	F_E (macular detachment)	F_F (macular pathology)
					All cases (n = 31)					
35	ABCDEF	13 92 d)	0 769	0 877 d)	31 20 d)	9 21 c)	6 91 b)	0 56	27 02 d)	5 09 b)
36	AEF	17 40 d)	0 659	0 812 d)	23 78 d)				20 87 d)	7 55 b)
37	ABEF	16 07 d)	0 711	0 843 d)	27 05 d)	7 99 [illegible])			23 17 d)	5 88 b)
38	ACEF	15 19 d)	0 700	0 837 d)	26 05 d)		9 47 [illegible])		21 33 d)	3 91 [illegible])
39	ABCEF	13 89 d)	0 735	0 857 d)	28 35 d)	8 37 c)	6 19 b)		23 11 d)	3 41 a)
40	ADEF	20 96 d)	0 [illegible]63	0 873 d)	32 98 d)			11 38 [illegible])	31 65 d)	7 84 c)

A blank F_{X_n} means that parameter was not considered in that ANOVA

Significance of F regression R and F_{X_n} (2 tailed tests) a) $P < 0.10$ b) $P < 0.05$ c) $P < 0.01$ d) $P < 0.001$

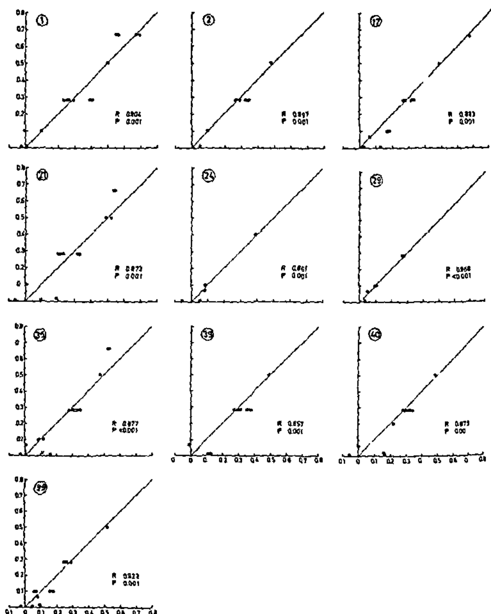


Fig. 1

Calculated final visual acuity (abscissa) vs. clinically observed final visual acuity (ordinate). Circled number on each panel represents the number of the equation in Table III from which the calculated acuities in that panel were determined (except for panel 99, for which the equation is not given). The 45 degree line in each panel represents identity between observed and calculated acuities. R is the coefficient of correlation between observed and calculated acuities.

lesions present at surgery only two cases would have had macular pathology The remaining raw data are as before Considering all six parameters and 31 cases MLR gave a highly significant regression explaining more than three quarters of the variation about the mean in the observed final acuities (ANOVA Eq Panel 35) Macular pathology still carried unique information (compare ANOVA 35 with ANOVA 8 of Table IA) SRF BuChE carried essentially all the information carried collectively by detachment duration and extent and additional information as well (ANOVAs 36–40) Final acuity could also be reasonably well predicted using the five clinical parameters (ANOVA Eq Panel 39) or patient age the two macular parameters and SRF BuChE (ANOVA Eq Panel 40)

A relationship between patient age and SRF BuChE seemed plausible on theoretical grounds (Kaufman & Podos 1973b) but by simple correlation analysis the association was weak and not significant ($r = 0.18$) However grouping

Table IV
Patient age vs SRF BuChE activity

Patient age	SRF BuChE activity (% plasma activity)		
	< 2.50 %	> 2.50 %	Mean activity ± SE
A *All cases (n = 31)*			
< 60 years	8	5	3.09 ± 0.74
> 60 years	4	14	5.03 ± 1.19
Mean age (years) ± SE	51.8 ± 5.2	65.8 ± 3.9 a)	
B *Cases with macular detachment but without macular pathology at any time (n = 15)*			
< 60 years	3	2	2.91 ± 0.60
> 60 years	1	9	6.31 ± 1.93 a)
Mean age (years) ± SE	51.7 ± 7.8	70.1 ± 3.3 b)	
C *Cases with macular detachment but without preoperative macular pathology (n = 29)*			
< 60 years	5	2	1.87 ± 0.48
> 60 years	4	11	5.30 ± 1.47 b)
Mean age (years) ± SE	58.8 ± 3.9	71.8 ± 3.1 c)	

Significant difference between means 2 tailed Student's t test
a) $P < 0.10$ b) $P < 0.05$ c) $P < 0.02$

Significance of distribution of cases by χ^2 test
A $P < 0.10$ B and C $P < 0.90$

the cases empirically according to these parameters revealed that patients over 60 years of age tended to have higher SRF BuChE levels than those under 60 and that patients with SRF enzyme activity > 2 50 % of their plasma enzyme activity were older than those in whom the SRF enzyme activity was < 2 50 % of the plasma activity (Table IV)

All the significance levels indicated in the tables are based on two tailed tests However in each instance the hypothesis being tested has been previously proposed on the basis of other data or on theoretical grounds (Kaufman & Podos 1973b) Therefore one tailed tests would be quite appropriate and the confidence levels would be twice as high (Diem & Lentner 1970)

Discussion

The conventional statistical approaches to identifying factors which influence final visual acuity in surgically reattached PRRD have major shortcomings and provide limited insights primarily because they consider only one suspect parameter at a time without taking others into account (see Introduction) Since multiple factors are involved at least some of which are interrelated (Kaufman & Podos 1973a b Kaufman 1975) a statistical method which can deal with multiple and related variables simultaneously would seem more appropriate As a first step in this direction MLR ANOVA was applied to a small series of cases all of which were "successful by the usual surgical criteria of retinal reattachment clear media and absence of severe vitreal or retinal pathology

Agreement between the clinically observed acuities and those calculated from the regression equations was generally reasonably good (Fig 1) Some of the scatter must be due to the random errors inherent in determining clinical acuity and clinical detachment characteristics The slight discrepancy (overestimation of low acuities and underestimation of high ones) could be due to different relationships between final acuity and the parameters in the different macular status groups omission of significant parameters or omission of power or product terms of the parameters considered Plotting the residual variations (acuity observed − acuity calculated) (Draper & Smith 1966) from Fq 2 against a few suspect power and product terms identified three products (BC DE DF) which might carry useful information about final acuity MLR ANOVA using the parameters A B F F BC DE DF G H gave R = 0 850 with R ≈ 0 922 (Fig 1 Panel 99) With more patients more parameters more precise measurements of acuity and clinical parameters and a more systematic approach to building the regression model (Draper & Smith 1966) it may be possible to

explain and predict final acuity in this disease extremely accurately Even with the primitive methods used here in a small series of patients and with all the assumptions and potential inaccuracies one could account for 85% of the variation about the mean of the final acuities Of course the main objective of the current study was not to construct a predictive model but rather to define relationships between final acuity and the individual parameters considered MLR ANOVA is well suited to this type of problem in which the parameters are all interrelated

In general older patient age greater detachment duration and extent higher SRF BuChE activity and preoperative macular detachment each exhibited a significant inverse relationship to acuity even in the absence of an overt macular lesion These parameters must therefore be associated with functional and/or anatomic macular changes too subtle to be detected by the clinical examination techniques employed Macular lesions significantly compromised acuity beyond the effects of the other parameters Duration of post surgical follow up and phakic/aphakic status had little influence on final acuity the long postoperative follow up (minimum 6 months mean 12 5 months) and the essentially clear lenses in the phakic eyes probably account for these findings

SRF BuChE activity was related to detachment duration and extent (Kaufman & Podos 1973a) and could substitute for both in influencing final acuity particularly in cases with macular detachment but without a visible macular lesion Older patients had more extensive detachments a greater tendency for the macula to detach and a tendency toward higher SRF BuChE activity

While some parameters carried unique information about final acuity at least part of the information carried by each parameter was also carried by one or more of the others This may indicate that there was a common pathophysiological process to which they were all related SRF BuChE activity reflects the degree of breakdown of the posterior segment blood ocular barrier (Kaufman & Podos 1973a b) The strong relationships between SRF BuChE activity and detachment duration and extent suggest that these two clinical parameters influence the state of that barrier (Kaufman & Podos 1973a b) That the SRF BuChE parameter carried the same information about final acuity as did the detachment duration and extent parameters collectively may mean that the influence of these two clinical parameters on final acuity is also related to the state of that barrier

We have previously hypothesized a pathophysiological sequence governing the visual outcome in PRRD in which the adequacy of the choroidal circulation and the blood ocular barrier of the posterior segment are of central importance (Kaufman & Podos 1973b) The current findings were all predicted by this hypothesis

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SYMPATHETIC NERVES TO THE RAT CORNEA

BY

TIMO TERVO and ARTO PALKAMA

The adrenergic innervation of the rat cornea was investigated by using the formaldehyde induced fluorescence (FIF) technique The fluorescent nerves were observed mainly in the corneal stroma. Either cervical sympathectomy or pre treatment with reserpine completely abolished the fluorescence of the adrenergic nerves of the cornea After a stereotactic coagulation of the ophthalmic division of the trigeminal nerve no adrenergic fibres were visible in the cornea and the number of the fluorescent iridic nerves was also reduced to a marked extent On the other hand ciliary ganglionectomy seemed to have no effect on the adrenergic fibres of the cornea

When the rats had been pre treated with a monoamine oxidase inhibitor nialamide, and noradrenaline not only was there an increase in the intensity of the specific fluorescence but also in the number of adrenergic nerves in the cornea

The epithelium was also shown to contain adrenergic nerves by administering high doses of nialamide combined with noradrenaline both intravenously as well as topically on the cornea under the protection of propranolol

It may be concluded that the rat cornea receives its adrenergic innervation along the posterior ciliary nerves The short ciliary nerves do not appear to carry sympathetic nerves to the cornea.

Key words adrenergic nerves – cornea – anatomy – FIF technique – intraepithelial nerve terminals – rat

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The sympathetic innervation of the cornea was first proposed by Boeke in 1935 By using the gold chloride impregnation technique he noticed that some of the nerves in the corneal stroma were thinner than others and assumed that these were sympathetic in origin Similar findings were later reported by Rodger (1950) On the other hand no adrenergic nerves were found by Zander & Weddel (1951) who used methylene blue staining

The development of the formaldehyde induced fluorescence (FIF) technique (Eränkö 1955 Eränko 1961 Falck & Torp 1961 Falck 1962) made possible the specific demonstration of sympathetic nerves Laties & Jacobowitz (1964 1966) and Ehinger (1964a b) described an adrenergic innervation of the cornea in some subprimate laboratory animals with the FIF technique

The cornea of adult primates is devoid of adrenergic innervation (Ehinger 1971) but adrenergic nerves have been observed in embryos (Ehinger & Sjoberg 1971)

The *present conception postulates that the anterior segment of the eye re* ceives its adrenergic innervation via the long ciliary nerves which are branches of the nasociliary part of the ophthalmic nerve (Duke Elder & Scott 1971) The short ciliary nerves which originate in the ciliary ganglion also seem to bring sympathetic fibres to the iris (Huhtala et al to be published)

The purpose of the present study is to give a description of the routes of the adrenergic nerves to the rat cornea The results are based on the observations made after various selective denervations

Material and Methods

Demonstration of adrenergic nerves

50 albino rats of both sexes of the Sprague Dawley strain were used in the study After killing the animal by rapid decapitation the eyes were enucleated and *the whole anterior segment of the eye was carefully excised with scissors* and subjected to the formaldehyde induced fluorescence technique for the de monstration of adrenergic nerves (Falck & Owman 1965 Eranko 1967)

Denervations

In order to demonstrate the origin of adrenergic nerves in the cornea the following denervations were carried out

1 Excision of the superior cervical ganglion of 12 rats This was invariably checked by the ptosis and miosis characteristic of Horner s syndrome

2 Extirpation of the ciliary ganglion of 10 rats The operation was performed subsequent to the cutting of the zygomatic arch and of the excision of the lateral part of the Harderian gland as described by Huikuri (1966) The operation was always followed by mydriasis

3 Stereotactic coagulation of the ophthalmic division of the trigeminal nerve distal to the Gasserian ganglion (Huhtala to be published) This operation was performed on 9 rats The successful outcome of the ophthalmic denervation was checked by the immediate loss of the corneal reflex and by the development of neuroparalytic keratitis during the subsequent few days Tarsorhaphy and the daily administration of eye drops containing chloramphenicol were used in order to avoid corneal ulcerations

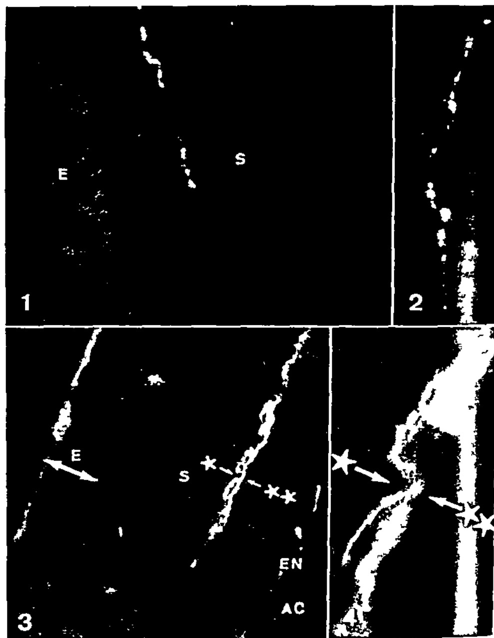
The time between subsequent denervations was from five to seven days and the animals were killed 6–21 days after the final denervation The excised superior cervical and ciliary ganglia as well as part of the ophthalmic nerve distal to the coagulation area were also subjected to histological investigation in some experiments All possible combinations of the denervations described above were also made

In order to check the specificity of the generated blue green fluorescence observed in the nerve fibres the following control experiments were carried out Four rats were pre treated with reserpine (Cipa Serpasil®) injected intra peritoneally (10 mg/kg 12 h before killing) to deplete catecholamines in the nerve fibres Different loading techniques were used to increase the catechola mine content of the adrenergic nerves 1 Three rats were injected with a mono amine oxidase inhibitor nialamide (Pfizer) in order to increase catecholamines in the nerve terminals The drug was introduced intraperitoneally (100 mg/kg one h before killing) 2 Four rats were treated both with nialamide (see above) and also with noradrenaline (0 1 mg/kg) injected into a tail vein 15 min before killing 3 Six rats were pre treated with nialamide 300 mg/kg ip and nor adrenaline 3 mg/kg iv including topical administration on the eye during the last twenty minutes prior to the killing of the animal Before noradrenaline infusion this group of rats was injected with propranolol (Inderal® Imperial Chemical Industries Ltd Great Britain) intravenously 2 mg/kg 30 min prior to killing The cervical sympathectomy was performed on two of the rats treated according to this technique

Results

In the normal rat cornea a few fluorescent adrenergic nerves were visible in the stroma as fine greenish fibres (Fig 1) The nerves were more numerous in the

peripheral than in the central part of the cornea The adrenergic nerves enter via the limbus and spread towards the central cornea Intraepithelial fibres were not visible in the non treated rats Most of the nerves were smooth in



appearance but small enlargements along the fibres could also be seen (Fig 2) The distances between the varicosities were relatively great The general tissue autofluorescence in the epithelium and endothelium was considerable The collagenous lamellas of the stroma also emitted a slight greenish autofluo rescence No catecholamine fluorescence was seen in the corneal endothelium

In the corneoscleral junction the fluorescent fibres could be seen around the blood vessels Numerous mast cells with bright yellow granular fluorescence were constantly seen in the neighbourhood of the limbal vessels

The chamber angle was negative even after loading with nialamide and noradrenaline

In stretch preparations of the cornea varicose adrenergic nerves were observed in the stroma (Fig 2) The tissue autofluorescence was disturbingly high and wrinklings of the tissue may cause arrors However these can be avoided by using a combined phase contrast and fluorescence microscope

Reserpine pre treatment completely abolished the fluorescence of the nerve fibres in the cornea (Fig 5) When the animals were pre treated with nialamide and noradrenaline the intensity of the specific blue greenish fluorescence sig nificantly increased as did the number of catecholamine containing structures (Figs 3 and 4)

Cervical sympathectomy abolished the fluorescence from the cornea and iris which owing to the large number of its adrenergic nerves was used as a reference tissue (Fig 7) On the other hand ciliarectomy seemed to have no effect on the corneal fluorescence (Fig 8)

Figs 1–4

Fig 1

FIF reaction in the rat cornea A fluorescent nerve fibre is seen in the stroma (S) The epithelium (E) shows moderate autofluorescence Magn x 550

Fig 2

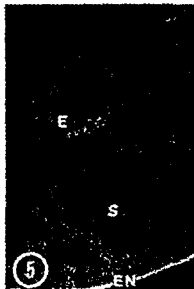
A stretched and air dried rat cornea Loading technique 2 A brightly fluorescent vari cose nerve fibre is seen against the black background of the corneal stroma. Magn x 400

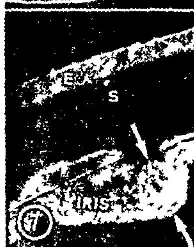
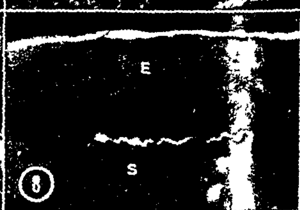
Fig 3

Rat cornea loaded according to technique 2 Two intensely fluorescent nerve fibres are seen in the stroma (S) One of the fibres (double star) is precisely focused whereas the other one (single star) is slightly out of focus Endothelium (EN) shows some non specific fluorescence as does the superficial border of the epithelium (E) The anterior chamber is marked by AC Magn. x 310

Fig 4

A higher magnification from the stromal area where the two fluorescent nerves are seen (stars) but the fibre marked with a single star is now in focus Magn x 1160


E
S
5
EN

E
S
6
EN

E
S
IRIS
7

E
S
8

E
S
9

T
E
S
10

Coagulation of the ophthalmic division of the trigeminal nerve reduced the number of fluorescent nerves in the anterior segment of the eye to a marked extent so that the cornea was totally negative and the majority of the iridic nerves also disappeared (Fig 9)

The effects of the denervations were unilateral in all cases clearly implying that the anterior eye segment does not receive any adrenergic innervation from the contralateral side

After treatment with loading technique 3 nialamide being administered intraperitoneally followed by both intravenous and topical administration of noradrenaline under propranolol protection intraepithelial nerves were also seen as thin varicose fibres (Fig 10) In some preparations these fibres were seen to arise from the larger nerve trunks of the stroma

The few intraepithelial fluorescent terminals were seen more commonly in the peripheral than in the central part of the cornea Loading with noradrenaline and nialamide increased the fluorescence in the endothelium and in the superficial parts of the epithelium A similar finding has been observed by Ehinger (1975)

Figs 5–10

Fig 5

Cornea from a reserpinized rat (100 mg/kg) All the fluorescent nerves have disappeared. Magn × 310

Fig 6

Cornea from a rat treated according to loading technique 1 The adrenergic nerve shows a normal FIF reaction Magn × 3 3

Fig 7

Cornea from a sympathectomized rat No fluorescent nerves can be observed in the cornea or in the iris (arrows) Magn. × 150

Fig 8

Cornea from a ciliarectomized (parasympathetic denervation) rat loaded as in Fig 6 contains fluorescent nerve fibres in the stroma Magn × 310

Fig 9

Cornea and iris (between arrows) from a rat 7 days after the ophthalmic neurotomy reveal no fluorescent nerves in the cornea but a moderate background fluorescence as well as a few fluorescent fibres can be distinguished in the iris Magn × 310

Fig 10

Cornea from a rat treated according to loading technique 3 a strongly fluorescent nerve terminal penetrates into the epithelium from the stroma (large arrow) The borderline between the stroma and the epithelium is indicated by small arrows Magn. × 590

Discussion

The formaldehyde induced fluorescence technique is well documentated (see e g Corrodi & Johnsson 1967 Bjorklund et al 1971) As the intensity of the generated fluorescence is comparable with the catecholamine content of the visualized nerves semi quantitative evaluations can also be made

In the present study the monoamine oxdidase inhibitor nialamide alone or with subsequent noradrenaline infusion clearly intensified the bluish green fluorescence of the nerves of the corneal stroma On the other hand reserpine completely abolished the specific fluorescence as did cervical sympathectomy From this result it can be stated unreservedly that the structures demonstrated are postganglionic adrenergic nerves

The ciliary ganglionectomy had no clear effect on the corneal adrenergic nerves which suggests that few if any of the adrenergic nerves of the cornea are distributed through the ciliary ganglion and along the short ciliary nerves to the cornea However the iris and ciliary body receive a minor part of their adrenergic innervation from the short ciliary nerves (Huhtala et al to be published) After stereotactic coagulation of the ophthalmic nerve no adrenergic nerves were observed in the cornea or around the limbal vessels Evidently the main sympathetic innervation of the anterior segment accompanies the long ciliary nerves which are branches of the ophthalmic nerve

The intraepithelial adrenergic nerve fibres observed in the embryonic corneas of many animal species disappear soon after birth (Ehinger 1966 Ehinger & Sjoberg 1971) Adrenergic intraepithelial terminals have also been found in the cornea of the human fetus too (Ehinger & Sjoberg 1971) In the present study intraepithelial nerve terminals were observed in adult rats after loading with both nialamide and a high dose of noradrenaline Propranolol was combined with nialamide and noradrenaline because the dose of noradrenaline was about hundred times the LD 50 for rat (Ylitalo & Ertama 1972)

It seems possible that under normal conditions the intraepithelial adrenergic nerves contain too low a concentration of the neurotransmitter to be visualized with the FIF technique As they disappear after cervical sympathectomy they appear to represent adrenergic nerve fibres

It has been assumed that the adrenergic nerves of the cornea are developmental remnants or that they possibly modulate the sensory transmission (Laties & Jacobowitz 1964) or regulate metabolism and mitotic activity (Ehinger 1964b Laties & Jacobowitz 1964) Intraepithelial adrenergic terminals have also been observed in the ciliary epithelium (Ehinger 1971 Uusitalo & Palkama 1971) It has been shown that adrenaline and cyclic AMP activate the ionic pump transporting chloride from the aqueous to tear side of the epithelium of

the rabbit and frog cornea (Zadunaisky et al 1973) Moreover the monoamine oxidase activity in the cornea has been histochemically localized to the epithelium in particular (Lukas & Čech 1965 Mustakallio 1967) Thus it can be suggested that the corneal adrenergic nerves might regulate ion and water transport through the epithelium

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The authors wish to express their gratitude to Dr K. T Huikuri M D for performing the ciliary ganglionectomies The eye research group is also grateful to Star Ltd Pharmaceutical Manufactures Tampere Finland for supplying us with laboratory animals We would also like to thank Prof B Ehinger M D for constructive criticism of the manuscript

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EFFECTS OF DENERVATIONS ON THE ACETYLCHOLINESTERASE-CONTAINING AND FLUORESCENT NERVES OF THE RAT IRIS

BY

ANTERO HUHTALA TIMO TERVO KAUKO T HUIKURI*
and ARTO PALKAMA

The thiocholine method for the demonstration of AChE containing fibres and the formaldehyde induced fluorescence technique for the visualization of adrenergic fibres were employed to study the innervation of the albino rat iris The following denervations were performed in order to verify the origins of different nerve types (1) extirpation of the ciliary ganglion (2) extirpation of the superior cervical ganglion, (3) stereotactic coagulation of the ophthalmic division of the trigeminal nerve and (4) all possible combinations of the above mentioned procedures

The denervations disclosed three main types of AChE containing nerves in the iris (1) nerve fibres degenerating after ciliary ganglionectomy (2) thick nerve bundles in the dilator region disappearing after trigeminal neurotomy and (3) fibres remaining intact after any type of denervation Cervical sympathectomy had no effect on AChE positive fibres

Under electron microscope AChE activity could be seen in the axolemma both in unmyelinated and in myelinated fibres

All fluorescent fibres vanished after ipsilateral cervical sympathectomy Most of these fibres also disappeared after trigeminal neurotomy and the remaining fibres degenerated after subsequent ciliary ganglionectomy

On the basis of the present findings the following conclusions can be drawn (1) Most AChE containing fibres of the rat iris originate in the ciliary ganglion (2) The majority of the myelinated sensory fibres of the rat iris also contain AChE (3) There is no AChE in the adrenergic fibres

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of the rat iris (4) All adrenergic fibres of the rat iris originate in the ipsilateral superior cervical ganglion and (5) these fibres enter the iris along with both the long and short ciliary nerves

Key words rat – iris – acetylcholinesterase – formaldehyde induced fluorescence – autonomic nerves – sensory nerves – trigeminal neurotomy – cervical sympathectomy – ciliary ganglionectomy

The thiocholine method for histochemical demonstration of acetylcholinesterase (AChE) has been used by many investigators to study the innervation of the rat iris (Csillik & Koelle 1965 Eränko & Raisanen 1965 Ehinger 1966a b Ehinger & Falck 1966) It is generally accepted that the *parasympathetic* cholinergic fibres of the rat iris are rich in this enzyme

On the other hand the results of previous investigations concerning the possible occurrence of AChE in the *sympathetic* adrenergic fibres of the iris are controversial Csillik & Koelle (1965) reported that some AChE containing fibres of the rat iris degenerated after extirpation of the superior cervical ganglion This finding has been supported by the denervation experiments of Eranko et al (1967) On the contrary Ehinger & Falck (1966) found no changes in the AChE containing fibres of the rat iris after superior cervical ganglionectomy More recently however Ivens et al (1973) with the electron microscope observed AChE reaction in some iridic axons containing small dense cored vesicles characteristic of adrenergic nerves

Several investigations have been performed demonstrating that AChE is also present in various components of the *sensory* nervous system (Koelle 1955 Abraham 1956 Coupland & Holmes 1957 Gerebtzoff & Bertrand 1957) Recently the rat iris has been shown to have a rich supply of sensory nerves (Saari & Johansson 1974 Huhtala 1975) However there are no studies concerning the AChE content of these nerves

All the fluorescent adrenergic fibres of the rat iris have been conclusively shown to degenerate after removal of the superior cervical ganglion (Falck 1962 Csillik & Koelle 1965 Malmfors 1965a b Malmfors & Sachs 1965 Eranko et al 1967) The ciliary ganglion of the rat also contains some fluorescent fibres (Huikuri 1966) However it has been reported that extirpation of this ganglion does not affect the fluorescent nerves of the iris (Ehinger & Falck 1966 Eranko et al 1967) Most adrenergic fibres seem to reach the cat iris *via* the ophthalmic division of the trigeminal nerve (Barlow & Root 1949 Johansson Huhtala & Saari 1975) It is not known if the ocular adrenergic fibres of the rat have a similar route

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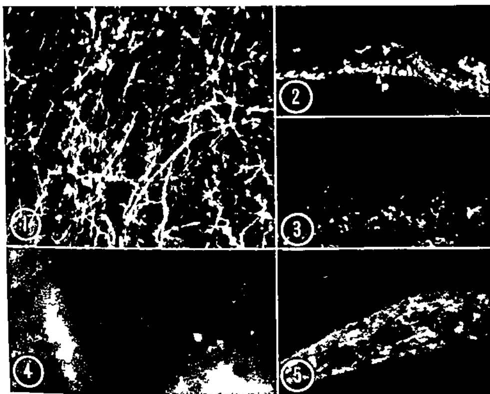
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Figs 1–5

Fig 1 Fluorescent (adrenergic) nerve fibres in the *dilator* area of a control iris An air dried stretch preparation × 150

Fig 2 Fluorescent (adrenergic) fibres in the *dilator* area of a control iris Most fibres are localized in the posterior part (p) of the iris A sagittal section from a freeze dried specimen × 160

Fig 3 Fluorescent (adrenergic) fibres in the *dilator* area of the iris 14 days after trigeminal neurotomy A clear decrease in the fluorescence activity can be seen A sagittal section from a freeze dried specimen × 160

Fig 4 An air dried stretch preparation from the iris seven days after superior cervical ganglionectomy All fluorescent fibres have disappeared × 320

Fig 5 Formaldehyde induced fluorescence in the rat iris after combined ciliary ganglionectomy and trigeminal neurotomy Almost all fluorescent fibres have disappeared A sagittal section from a freeze dried specimen × 240

Demonstration of AChE-containing fibres After killing the rat both eyes were enucleated and the irises dissected independently Each iris was cut diagonally into two equal parts One half of the iris was used to demonstrate AChE activity (Lewis & Shute 1966) and the other half was used for demonstration of one of the segments were immersed in liquid nitrogen and subsequently freeze

The part of the iris subjected to the light microscopical demonstration of AChE activity was fixed in 2.5 % glutaraldehyde buffered with 0.2 M phosphate buffer pH 7.2 for 1 h For the electron microscopy the specimens were fixed in a similar solution for 3 h After fixation the irises were rinsed overnight in the same buffer at 4 C

Before incubation with the substrate (acetylthiocholine iodide Fluka AG Bucks) the preparations were pre incubated for 30 min in the buffer solution without the substrate This pre incubation medium contained 0.02 mM tetra isopropylpyrophosphoramide (iso OMPA) This inhibitor was also used in the same concentration in the substrate containing incubation medium The incubation was carried out at 4 C for 4 h

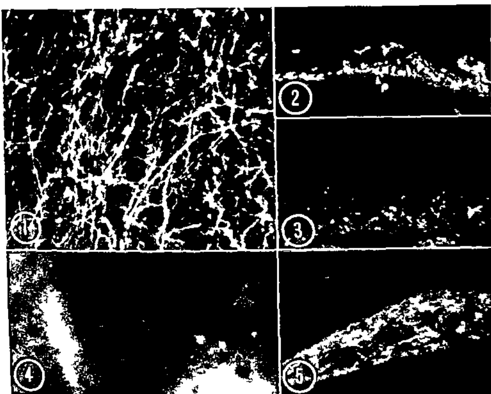
For the light microscopy stretch preparations were mounted on slides in glycerol jelly

For the electron microscopy specimens from control irises were postfixed in 1 % osmium tetroxide buffered with 0.1 M phosphate buffer at pH 7.2 After dehydration with ethyl alcohol the specimens were embedded in Epon Araldite

Demonstration of the adrenergic fibres The adrenergic nerves were demonstrated by using the formaldehyde induced fluorescence technique (Falck & Torp 1961) Immediately after cutting the iris into two segments small sections of one of the segments were immersed in liquid nitrogen and subsequently freeze dried for 7 days at –45 C in a vacuum of 10 –10^{4} mmHg The freeze dried specimens were exposed to formaldehyde vapour generated from paraformaldehyde powder The preparations were embedded in paraffin and 5 μm sections were viewed under a fluorescence microscope equipped with a HBO 200 mercury lamp (Osram) and a Ploem (1971) epi illuminator The following filters were used BG 38 two BG 3 a TAL 405 interference filter the dichroic mirror TK 455 with protecting filter K 460 and a K 470 ultraviolet filter above the objective (all filters by Schott & Gen Mainz)

In some experiments the iris segment was treated as a stretch preparation The tissue was dried with a piece of blotting paper and exposed to formaldehyde vapour without previous freeze drying

Controls for the histochemical methods Non specific cholinesterase of the normal iris was demonstrated using butyrylthiocholine iodide (Fluka AG Bucks)



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a substrate and 0 02 mM 284 C 51 (1 5 bis (allyl dimethylammoniumphenyl) ntan 3 onediiodide) as a selective inhibitor for acetylcholinesterase in the e incubation and incubation solutions The incubation was performed at 4°C r 4 h at pH 7 0

In order to control the specificity of the reactions the inhibitor 284 C 51 as also combined with the substrate acetylthiocholine iodide and iso OMPA ith butyrylthiocholine iodide Moreover both the inhibitors (iso OMPA and 34 C 51) were used together either with acetylthiocholine or butyrylthiocholine dide as a substrate

The specificity of the bluegreen fluorescence due to the amines in the adre ergic fibres was controlled by means of the following pharmacological proce ires (1) reserpin (Serpasil® Ciba) was injected intraperitoneally (10 mg/kg h before killing) into four unoperated rats in order to deplete catecholamines om the adrenergic nerve fibres (2) two normal rats were pretreated with a onoamine oxidase inhibitor nialamide (Pfizer) (100 mg/kg ip 1 h before lling) in order to increase the catecholamine content in the adrenergic nerves

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Figs 6–8

g 6 A AChE containing fibres in a stretch preparation from a control iris Note the ick AChE containing bundles (b) in the *dilator* area as well as the fine fibres (f) parate fibres cannot be discerned in the intensely stained *sphincter* (s) area ×23

g 6B A higher magnification from the *sphincter* (s) area of the same iris as in g 6A ×77

g 6C A higher magnification from the *dilator* area of the same iris as in Fig 6A owing a dense network of fine AChE containing fibres (f) as well as the thick nerve ndles (b) ×77

g 7A AChE containing fibres in the iris 21 days after ipsilateral ciliary ganglionec my The staining of the *sphincter* (s) is weaker than in the normal iris There are ense intact nerve bundles (b) visible in the *dilator* region ×23

g 7B A higher magnification from the *sphincter* (s) area of the same iris as in g 7A ×77

g 7C A higher magnification from the same iris as in Fig 7A showing intact thick rve bundles (b) in the *dilator* area ×77

g 8A AChE reaction in the iris 21 days after trigeminal neurotomy Thick nerve ndles have disappeared from the *dilator* area but the staining of the *sphincter* (s) oks normal ×23

g 8B A higher magnification of the same iris as in Fig 8A showing a normal ain n n the *sphincter* (s) ×77

g 8C A higher magnification of the same iris as in Fig 8A There are no AChE con ning thick nerve bundles visible in the *dilator* area ×77


b
s
7A
b
8A
6B
s
8B
s
7C
b
8C
b

Results

Control (normal) iris Under light microscope the AChE containing nerves seemed to enter the ciliary root of the iris as thick bundles at several points From a circularly arranged plexus in the ciliary border of the iris the bundles ran radially to the dilator region where they formed a loose circular plexus (Fig 6A) A dense network of fine AChE positive fibres could be seen throughout the dilator region These fibres mainly ran radially extending to the sphincter area (Figs 6A C) The AChE reaction was most intense in the sphincter region Here single nerve fibres could rarely be discerned under low magnifications (Fig 6B)

Under electron microscopic examination the AChE reaction was seen on the axolemma of unmyelinated fibres (Fig 9) Also most myelinated fibres had intense staining for AChE on their axolemma (Fig 9) Some myelinated fibres were stained only partially and a small number were not stained at all

No AChE containing fibres were found around the blood vessels of the iris



Fig 9

An electron micrograph showing AChE reaction (arrows 1 and 2) on the axolemma of both myelinated (presumptive sensory) and unmyelinated (presumptive parasympathetic) fibres in the normal rat iris × 28 000

Under light microscope the non specific cholinesterase activity like the AChE activity seemed to be mainly localized in the nerves The result was similar when 284 C 51 was used as an inhibitor and acetylcholine iodide as a substrate When the incubation was performed at pH 7 0 and at 4 C for 4 h with butyrylthiocholine iodide as a substrate and iso OMPA as an inhibitor the localization of the reaction was identical to the AChE reaction but much weaker When the irises were incubated with one of the two substrates in the presence of both inhibitors only slight non specific staining was seen inside the blood vessels

In the air dried stretch preparations used for the demonstration of the adrenergic nerves varicose fluorescent fibres were seen as a dense network in the dilator region (Fig 1) Most fibres were oriented radially Moreover the spincter was supplied by the adrenergic fibres here most fibres had a circular arrangement. There was a dense plexus of fluorescent fibres around the blood vessels In tissue sections the adrenergic fibres were distributed most abundantly in the posterior part of the iris (dilator muscle) (Fig 2)

After reserpine pre treatment all fluorescent fibres disappeared from the iris Treatment with nialamide strongly increased the intensity of the fluorescence reaction

Ciliary ganglionectomy Extirpation of the ciliary ganglion caused a clear decrease of the AChE reaction especially in the sphincter area of the ipsilateral iris (Figs 7A and B) This effect could be seen from the fourteenth day after the denervation Thick AChE positive bundles in the dilator region remained intact (Figs 7A and C)

In most experiments some reduction in the number of adrenergic fibres could also be seen under the fluorescence microscope

Superior cervical ganglionectomy No degeneration was observed in the AChE containing fibres of the iris after this operation On the other hand a total disappearance of adrenergic fibres was noted seven days after the denervation in the ipsilateral iris (Fig 4)

Trigeminal neurotomy After coagulation of the ophthalmic nerve the AChE containing dense nerve bundles appearing in the dilator region of the control iris (Figs 6A and C) were not observed in the denervated iris (Figs 8A and C) The sphincter area stained for AChE with normal intensity after this denervation (Figs 8A and B)

Most adrenergic fibres disappeared from the denervated iris after trigeminal neurotomy (Fig 3)

Effects of combined denervations The effects of all denervation combinations on AChE containing nerves of the iris were simple summations of the separate denervations when ciliarectomy was combined with trigeminal neurotomy both of the changes described above occurred only few AChE containing fibres remained visible (Table I) Cervical sympathectomy had no additional effect on the AChE containing nerves when combined with either ciliarectomy and/or trigeminal neurotomy (Table I) When ciliary ganglionectomy was performed on the same animals together with coagulation of the ophthalmic nerve a total disappearance of adrenergic fibres could be observed in the ipsilateral iris (Fig 5 Table I) When cervical sympathectomy was combined with ciliary ganglionectomy and/or with trigeminal neurotomy the results were similar to those of sympathectomy alone (Table I)

Table I

Effects of denervations on different nerves of the iris

Denervations (explanation for codes in Fig 10)	Types of nerves			
	Fluorescent (adrenergic) fibres	AChE containing nerves		
		Fine fibres in sphincter area	Fine fibres in dilator area	Thick bundles in dilator area
CG	++(+)	+	+	+++
SCG	–	+++	+++	+++
TN	+	+++	+++	(+)
CG SCG	–	+	+	+++
CG TN	–	+	+	(+)
SCG TN	–	+++	+++	(+)
CG SCG TN	–	+	+	(+)

The fluorescence intensity and the AChE activity were registered from +++ (normal) to – (negative)

Discussion

The present observation that superior cervical ganglionectomy did not affect the AChE positive fibres of the rat iris is in agreement with the findings of Ehinger & Falck (1966) Degeneration of most AChE containing nerves in the iris after ciliary ganglionectomy confirms that majority of them are parasympathetic in character The thick AChE positive bundles remaining intact in the dilator region after ciliary ganglionectomy seem to contain sensory trigeminal fibres because they disappeared after ophthalmic neurotomy A further evidence for the presence of AChE in the sensory fibres of the iris is the AChE precipitation seen with electron microscopy on the axolemma of myelinated nerves

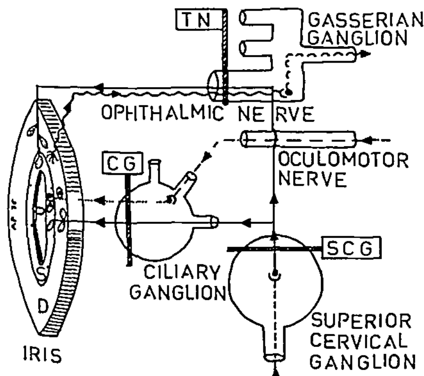


Fig 10

Schematic illustration of adrenergic (preganglionic — -- and postganglionic ——) and AChE containing (parasympathetic preganglionic – – – – parasympathetic postganglionic sensory preganglionic ∿∿∿ and sensory postganglionic ⌒⌒⌒) nerve fibres of the iris Denervations indicated by C G (ciliary ganglionectomy) S C G (superior cervical ganglionectomy) and T N (trigeminal neurotomy)

which on the other hand have been shown to originate exclusively from the trigeminal nerve (Huhtala 1975) The biological function of AChE in the sensory nerves is open to question It may indicate that acetylcholine is a chemical mediator of sensory impulses in the rat iris as it seems to be in the rabbit cornea (Fitzgerald & Copper 1971) Some AChE activity seen in the thin iridic nerves after combined ciliary ganglionectomy and ophthalmic neurotomy may indicate that the rat iris receives some postganglionic parasympathetic fibres which do not originate from the ciliary ganglion.

In the control experiments carried out in order to specify the cholinesterase activity it could be observed that the enzyme on the axonal membranes of both the unmyelinated and myelinated fibres was totally inhibited by 284 C 51 Thus the enzyme appeared to be acetylcholinesterase However this enzyme was also capable of hydrolyzing butyrylthiocholine iodide in the presence of iso OMPA (0 02 mM) at pH 7 0 when the incubation time was 4 h This finding supports the observations of Eranko & Eranko (1974)

The majority of the fluorescent nerves seem to travel to the rat iris *via* ophthalmic nerve since most of them disappeared after trigeminal neurotomoy This observation is parallel to the previous reports concerning the sympathetic fibres of the cat eye (Barlow & Root 1949 Johansson Huhtala & Saari 1975) All those fluorescent fibres of the iris which remained intact after trigeminal neurotomy disappeared after subsequent ciliary ganglionectomy These fibres seem to constitute the sympathetic root of the ciliary ganglion possible entering from the cavernous plexus along with blood vessels and leaving the ciliary ganglion *via* the short ciliary nerves (Fig 10) Those fluorescent nerves which join the ophthalmic nerve evidently run to the eye with the long ciliary nerves and/or blood vessels (Fig 10)

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THE NATURE OF CAPSULAR INCLUSIONS IN LENTICULAR CHALCOSIS

Report of a case

BY

JOHAN H. SELAND

A case of lenticular chalcosis has been studied where the accidentally implanted brass fragment had been removed 2 years prior to extraction of the lens. Characteristic capsular inclusions were found which did not contain copper. The inclusions probably consisted of a lipoid material.

Key words: Lens capsule – chalcosis – sunflower cataract – copper – electron microscopy.

The term Scheinkatarakt (Pseudocataract) was coined by Purtcher (1918) to describe a type of cataract which develops as a sequel to accidentally implanted copper in the eye. The reason for this name was that the cataract could only be seen in oblique illumination and had little or no influence on visual acuity. The histological picture of lenticular chalcosis was originally described by Jess (1922). Located near the epithelial cells in the anterior lens capsule he found a pigment zone which consisted of numerous small round particles. In the posterior part of the lens he found copper impregnation of the cortex adjacent to the capsule. Since the first description of this syndrome it has always been

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assumed that the capsular particles found in chalcosis were some form of copper precipitate

Siemerling & Oloff (1922) described a similar type of cataract in a patient with Wilson's hepato lenticular degeneration and they suggested a common etiology The great majority of research on the "ocular copper syndrome" has concerned material from patients with Wilson's disease The work has usually been centered on the changes in the corneal basement membrane which result in the Kayser Fleischer ring The morphological picture seen in Descemet's membrane cannot be distinguished from the changes seen in the lens capsule (Tso et al 1975) Several opinions as to the nature of the corneal and lenticular pigments in Wilson's disease have been put forward since the original discovery Some of the early workers suggested haemoglobin derivative (Salus 1908 Fleischer 1922) urobilin (Hessberg 1925) a lipoid soluble pigment (Metzger 1924) and silver (Rumpel 1913 Vogt 1929)

These differences of opinions were settled by Gerlach & Rohrschneider (1934) who were able to demonstrate increased amounts of copper in the eye in Wilson's disease thus supporting the original suggestion of Siemerling & Oloff This has later been confirmed in a number of reports (Brand & Takats 1951 Uzman & Jakus 1957 Harry & Tripathi 1970 Kanai et al 1974)

In later years reports of the "ocular copper syndrome" in multiple myeloma have been published (Ellis 1969 Lewis et al 1975) The findings here do not differ from Wilson's disease or chalcosis due to intraocular foreign bodies Hanna & Fraunfelder in 1973 published ultrastructural lens changs in two cases of chalcosis due to longstanding retention of foreign bodies They demonstrated extensive changes with dark staining areas in the lens capsule and epithelial cell damage The changes were most pronounced in the capsule which covered cells with a normal appearance while the capsule near destroyed or damaged cells was less transformed Uzman & Jakus (1957) have tabulated the properties of the "pigment inclusions" found in the Kayser Fleischer corneal ring

1 A formaldehyde fixed speciment will exhibit a strong positive rubeanic acid reaction indicating the presence of copper in the "pigment" inclusions

2 The inclusions and the copper reaction disappear after primary fixation with organic solvents

3 Weak mineral acids have no effect on the copper reaction of the specimens

4 The rubeanic acid copper reaction is abolished by treatment with a chelating agent e g sodium versenate

It has also been shown that copper occurs in large amounts outside the pigment areas (Brandt & Takats 1951 Uzman & Jakus 1957) but this diffusely distributed copper has different chemical properties In its native state it is unaffected by organic solvents but dissolved by weak mineral acids water and sodium versenate

The purpose of this study has been to investigate the changes seen in the lens capsule in chalcosis to compare them with earlier findings (Hanna & Fraunfelder 1973) and see if removal of the copper stimulus has any influence on the changes

Material and Methods

A healthy 20 year old male in 1965 received a perforating injury of his right eye caused by cartridge explosion A brass fragment (1 × 1 5 mm) perforated the sclera and lodged near the retina at the posterior pole The vision was 6/6 on admission but deteriorated later due to retinal reaction The fragment was not removed as the operative risk was considered greater than the benefit one might expect 18 months after the accident a sunflower cataract was noted The foreign body had at that time moved towards the periphery and 5 years after the original accident the metal fragment presented itself in the anterior chamber angle and was extracted by operation No Kayser Fleischer ring was seen in the cornea but the lens was subluxated and one also noted a sclerosing cataract in addition to the yellow green sun flower Two years after the foreign body extraction the lens was removed because of cataract and fixed in phosphate buffered gluteraldehyde 3 % After post fixation in osmium tetra oxide dehydration was performed through alcohol to propylene oxide and the lens cortex with its capsule was embedded in Epon 812 The posterior pole of the capsule was unfortunately damaged in the preparation process

The material was subjected to the following tests

Ordinary transmission electron microscopy (TEM) was performed with a Philips 300 EM apparatus using 700 Ångstr thick sections Some of the sections were stained with lead and uranyl

Histochemical localisation of copper was performed according to the method of Okamato Utamura modified by Uzman (1956) using a cataract lens and known metallic copper as controls

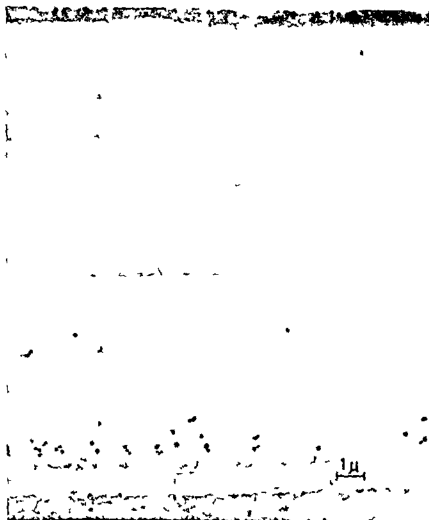


Fig 1
Section through the anterior pole × 4,500 Note osmiophilic particles throughout the capsule except in a 0 9 μ zone adjacent to the epithelial cells

Energy dispersive X ray analysis was performed with a ORTEC 7000 series Si (Li) X ray detector mounted on a Jeol U3 scanning electron microscope The unstained 1 μ thick sections were mounted on palladium grids in aluminium holders

Electron diffraction study using 1500 Angstr thick sections was performed on Philips EM 300 electron microscope



Fig 2

Section through anterior capsule 2 mm from the anterior pole x 40 000 Note the homogenous non particulate zone and the regular size sequence of the particles with the small 80 Å particles innermost increasing to a diameter of 1600 Å more superficially

Results

On electron microscopy round electron dense osmiophilic particles were seen in the anterior capsule (Fig 1) The particles had a diameter ranging from 80 to 2000 Å The particles were separated from the epithelial cells by a 1 1 μ thick zone at the anterior pole (Figs 1 2) and up to 3 μ thick at certain areas near the equator

There seemed to be a strict sequence as to the particle size and their prox

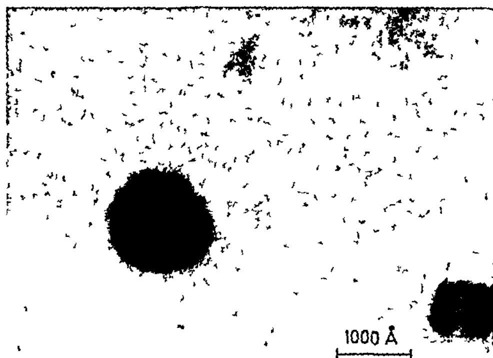


Fig 3
Enlargement of particles × 180 000 Note the irregular surface outline of the two particles

imity to the epithelial cells The smallest particles were found nearest the epithelium and the larger particles were located superficial to these (Fig 2) Medium size particles could be found high up even near the surface of the capsule (Fig 1) The small particles were roundish and uniformly stained but the larger particles had a more irregular surface outline (Fig 3)

The results of rubeanic acid histochemistry were undecisive and were considered equivocal

The energy dispersive X ray analysis instrument failed to detect any significant amount of copper as the spectra obtained from the particle zone and the particle free zone were almost identical possibly with a slightly more pronounced osmium deflection at 8 91 K e V in the particle zone (Fig 4)

Electron microscopic diffraction studies on the electron dense particles revealed no characteristic diffraction pattern

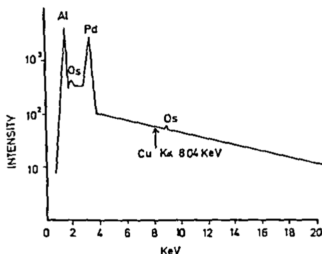


Fig 4

Energy dispersive X ray analysis Except for a slightly less conspicuous Os peak at 8.91 k e V the spectra obtained outside the particulate zone were identical to those obtained in the region of the particles No trace of Cu at 8 04 k e V

Discussion

In vitro radio isotope experiments have shown that the lens capsule is produced by epithelial cells (Young & Ocumpaugh 1966 v Sallmann et al 1969 Hanna & Fraunfelder 1973) The fact that the whole capsule was impregnated with electron dense particles except in a distinct layer adjacent to the epithelial cells probably indicates that particle free zone represents the capsule produced in the two year period that elapsed between the removal of the copper and the extraction of the lens

A non particular zone has also been described in Wilson s disease (Uzman & Jakus 1957 Harry & Tripati 1970) while other workers have found capsular particles at the cellular border in this disease (Johnson 1973) and in exogenous chalcosis (Hanna & Frauenfelder 1973)

The particles were probably produced by the cells while under influence of copper and this supports the investigation of Hanna & Fraunfelder (1973) who only found capsular changes near the cells which appeared normal and presumably were able to produce capsular substance It has been shown that copper has a very noxious effect on several epithelial cell enzymes thus causing an abnormal metabolism (Awasthi et al 1975) This cell damage may well

explain the appearance of abnormal capsular substance — e. g electron dense particles

This investigation fails however to support the data from the Kayser Fleischer ring as to the content of copper in the electron dense particles in the basement membrane (Harry & Tripathi 1970 Kanai et al 1974 Tso et al 1975) It is known that the copper present in these particle is easily exchanged by chelation (Uzman & Jakus 1957) In view of the fact that this lens was metabolically active and producing capsular substance two years after the copper stimulation had been removed it is reasonable to suggest that if any copper was originally present it had disappeared as a result of an equilibration exchange process without affecting the morphological appearance of the particles The striking size sequence of the particles probably indicate that very small particles are produced by the cells but these may coalesce forming larger and more irregularly outlined complexes The particles seem to mingle intimately with the capsular stroma and displacement or wedging of the capsular lamina could not be found in any of the sections The observation of medium size particles throughout the greater part of the central capsule may indicate some form of self propagation A possible explanation for this may be the action of electrochemical forces Kinsey & McGrady (1971) have analysed the membrane potential of the lens capsule and found a difference of —40 mV

The electron dense particles observed in the anterior lens capsule in chalcosis exhibit the following characteristics in addition to those listed by Uzman & Jakus (1957) for Descemets membrane

1 They probably contain copper when produced by the epithelial (or endothelial) cells The copper may disappear naturally following withdrawal of the copper stimulus without affecting the marked electron density

2 Newly formed particles are small but may coalesce into larger aggregates and may possibly exhibit some form of self propagation

The type of substance to fulfil most of these requirements is probably of lipoid nature thus supporting the views of Metzger (1924) Brand & Takats (1951) and Uzman & Jakus (1957) It also confirms that the colours of the sun flower cataract are not due to copper complex impregnation of the basement membrane but are purely an optical interference phenomenon

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MELANOTROPIC DRUGS AND RETINAL FUNCTIONS

I Effects of quinine and chloroquine on the sheep ERG

BY

BERIT CALISSENDORFF

The present work is the first in a series of investigations on the effects of melanotropic drugs on retinal functions The changes in the conventional ERG of the dark adapted intact sheep eye were studied after iv administrations of quinine and chloroquine. Both drugs influenced the ERG in principally the same way Small doses changed only the *c* wave amplitude which began to oscillate after a delay of about 1 hour Larger doses had an immediate effect on both the *b* and *c* waves The *b* wave amplitude dropped and the *c* wave showed an initial peak followed by oscillatory changes about 1 h later These late changes were similar to those observed after administration of small doses of the drugs
The present results indicate that small doses of quinine and chloroquine have a delayed effect on the pigment epithelial cells while larger doses exert a more immediate and general retinotoxic effect

Key words chloroquine – quinine – sheep – electroretinography – *c* wave – retina – pigment epithelium

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It is well known that certain antimalarial drugs have side effects which might influence the visual functions The first cases of visual disturbances caused by quinine were reported more than a century ago (v Graefe 1857) The synthesized antimalarial compounds (i e chloroquine and its derivatives) were not implicated as retinotoxic until they were used in long term treatment of rheumatic diseases In 1957 Cambiaggi described the first case of retinal lesion due to synthesized antimalarial drugs The association of retinopathy with chloroquine was definitely shown in many subsequent reports Reviews of the toxic effects of chloroquine on the eye have been published by among others François & De Becker (1965) Meier Ruge (1965) Voipio (1966) Bernstein (1967) Boke et al (1967) Nylander (1967) and François et al (1972)

The exact site of toxic action of antimalarial drugs in the eye is not known Autoradiographic studies on the chloroquine distribution have shown that the drug has melanin affinity and that this affinity extends to the uveal tract (Potts 1961 Lindquist 1973) Many investigators have considered the accumulation of chloroquine or its metabolites in the melanin of the retinal pigment epithelial as an important factor in the production of retinopathy (Potts 1964 Meier Ruge 1965 1967 Babel & Englert 1969 Ramsey et al 1970) The assumption of drug accumulation as a primary cause of retinal damage is further supported by the clinical observations that chloroquine retinopathy is related to dosage levels and duration of therapy (Voipio 1966 Bernstein 1967 Nylander 1967 Crews 1969)

Some ultrastructural studies of chloroquine retinopathy have shown accumulation of the drug and changes in the pigment epithelial layer (Bernstein & Ginsberg 1964 Meier Kuge 1965 1969 Adlakha et al 1968 Rosner & Legros 1970) However in these studies the changes were not confined to the pigment epithelial cells Recent studies in cats (Berson 1970 Smith & Berson 1971) seem to indicate that the initial damage occurs in the photoreceptors

From the above mentioned observations it may be concluded that functional studies on chloroquine retinopathy should be focused not only on the neuro retina but also on the pigment epithelial layer The activity of this layer is known to be reflected in the c wave of the ERG (Noell 1954 Brown & Wiesel 1961 Steinberg et al 1970 Schmidt & Steinberg 1971) Thus it seems likely that drugs affecting the pigment epithelial cells will influence the c wave of the ERG a fact that has been shown in experimental studies (Hommer et al 1968 Junemann & Schultze 1968) The results of these reports are somewhat conflicting as Junemann & Schultze (1968) found that both quinine and resochin a chloroquine derivative altered the c wave while Hommer et al (1968) found that only quinine resulted in such changes The results might partly be explained by variations in technique and species differences

The present work was undertaken to evaluate the acute effects of quinine and chloroquine on retinal functions by use of an ERG method which allows long term corneal d.c registrations from the intact sheep eye Special interest was centered on the activity in the pigment epithelial layer represented by the *c* wave of the ERG and consideration was made for the amplitude variations of the normal *c* wave (Calissendorff et al 1974)

Methods

The d c ERG recording technique used in these experiments was originally described by Knave et al (1972) and further developed by Calissendorff et al (1974)

Animals

Experiments were performed on 12 sheep in the dark adapted state Each sheep was anesthetized (Pentothalsodium® 20 mg/kg b w iv) and immobilized (gallamine triethioidide Flaxedil® iv) The animal was then tracheotomized and artificially ventilated The femoral arterial blood pressure was continuously recorded and the body temperature was maintained at its normal 39°C A reference electrode was placed subcutaneously at the upper bony margin of the orbit The pupil was dilated with 0 5 % Tropicamide 1 % Homatropin and 1 % Atropin eye drops and a scleral contact lens with recording electrode was applied Cornea and conjunctiva were anesthetized with 2 % Tetracaine eye drops and all wound margins as well as pressure points were repeatedly infiltrated with local anesthetic (2 % Xylocaine®)

Stimulating and recording techniques

Light *stimulation* was provided by a Xenon arc lamp (*Zeiss 900 W*) *Stimulus* duration was 1 sec and stimulus intensity 4 5–5 0 log units above the *b* wave threshold *of the dark* adapted eye The recording and reference electrodes were matched calomel half cells The electrodes were connected with saline bridges in polyethylene *tubes to the differential inputs of a lowdrift d c amplifier* The potentials were low pass filtered (500 Hz cut off 18 dB/octave) and fed into an *Intertechnique DIDAC 800 signal averager The amplitude registrations* were calculated from the means of two consecutive summated responses The amplitudes of the *a* and *c waves were measured from the isoelectric line and the b* wave from the trough of the *a* wave

Experimental procedure

The animal was kept in darkness for a period of about 12 hours before the actual experiment The dissection was performed in dim light in order to main tain full dark adaptation After application of electrodes the sheep was kept in darkness for about 3 hours According to earlier studies (Calissendorff et al 1974) the c-wave amplitude reaches a "steady state" after about 100 minutes of repeated stimulation To obtain this steady state the eye was stimulated at intervals of 30 seconds for about 2 hours The drug was not injected until the c wave amplitude had reached its "constant level

The drugs used were chloroquine phosphate and quinine hydrochloride The various doses (0 05–5 0 mg/kg b w) were diluted in 20 ml saline solutions and slowly administered iv over a 5 to 10 min period

Results

The retinal effects following iv administration of chloroquine and quinine were studied in 9 experiments – 5 with chloroquine and 4 with quinine No essential differences were found between the two drugs in terms of their effects on the ERG

The results to be presented illustrate the findings from two different experi ments (1) after administration of a small and (2) after administration of a relatively large dose of chloroquine

Fig 1 shows the ERG changes induced by iv injection of 0 25 mg/kg b w chloroquine (arrows) The amplitude of the *a* *b* and *c* waves are graphically illustrated as a function of time In contrast to the *c* wave the *a* and *b* wave amplitudes remained unchanged during the entire time of registration After about 60 min following each injection the *c* wave started to change in am plitude the variations resembling damped oscillations with a frequency of about 2 hour Furthermore a slow increase of the *c* wave amplitude was recorded in this experiment However this slow increase had been observed before the first injection and moreover it was not seen in all experiments It is therefore pos sible that this increase represented the slow oscillation of the *c* wave amplitude described by Calissendorff et al (1974)

In the experiment illustrated in Fig 2 a dose of 5 mg chloroquine/kg b w was injected twice (arrows) The *a* wave was relatively unaffected although small immediate reductions in the amplitude were demonstrated Almost imme diately after the first injection the *b* wave amplitude rapidly decreased and

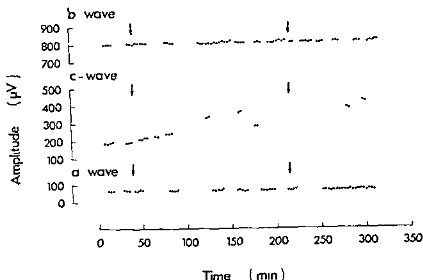


Fig 1

Effect of small doses of chloroquine on the *a* *b* and *c* wave amplitudes of the dark adapted sheep eye Two iv injections of 0 25 mg/kg b w chloroquine were given after 40 and 210 min respectively (arrows) Stimulus intensity 4 5 log units above *b* wave threshold Stimulus duration 1 sec

then remained at a level about 100 μV lower than that prior to the drug ad ministration The *c* wave amplitude showed a small initial drop followed by a large transient increase and then reached a level only somewhat lower than that before the injections After these initial transient changes the *c* wave amplitude remained constant for about 60 min and then as can be seen in the diagram began to oscillate with a frequency of about 2–3/hour

The other experiments showed depending on dose of the administered drugs a reaction pattern of the ERG similar to those illustrated although the animals varied with regard to sensitivity As for the *c* wave oscillations described the smallest dose producing an effect was 0 1 mg/kg b w The smallest dosage found to influence both the *b* wave and *c* wave amplitudes (see Fig 2) was 3 mg/kg b w There was no certain relationship between the magnitude of the *c* wave changes and that of the *b* wave Furthermore in some of the experi ments especially with doses of 3–5 mg/kg b w the decreased *b* wave showed a tendency to recover with time

In studies on the toxic effects on retinal fun tions the possibility of altered circulatory system conditions must be taken into consideration Knave & Persson

(1974) found that small and moderate changes in blood pressure did not influence the ERG In pilot studies it was observed that doses of about 10 mg/kg b w or larger had significant effects on the circulatory system In the present study only doses up to 5 mg/kg b w were included thus excluding secondary influences due to circulatory effects

Discussion

The results presented show that large doses of quinine and chloroquine influenced both the *b* and *c* wave and sometimes also the *a* wave indicating a widespread retinotoxic effect Small doses of the drug (less than 3 mg/kg b w) caused changes only in the *c* wave indicating an influence mainly restricted to

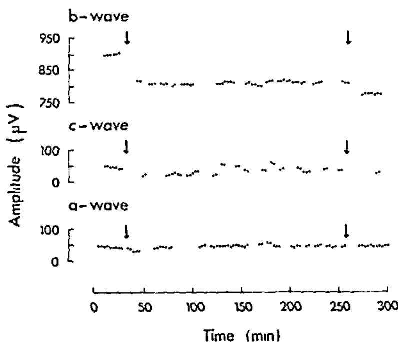


Fig [illegible]

Effect of relatively large doses of chloroquine on the *a* *b* and *c* wave amplitudes of the dark adapted sheep eye Two iv injections of 5 mg/kg b w chloroquine were given after 35 and [illegible]5 min respectively (arrows) Stimulus intensity 4.5 log units above *b* wave threshold Stimulus duration 1 sec

the pigment epithelium The results of this study in many ways support previous findings Hommer (1968) described three patients in whom the ERG was re corded immediately following ingestion of massive doses of quinine Each patient showed a marked initial reduction in the *a* and *b* waves The *a* wave recovered quickly The *b* wave however recovered more slowly and finally declined Similar findings were also described in experimental studies in rabbits (Junemann & Schulze 1968 Cibis et al 1973) and cats (Hommer et al 1968 Berson 1970) As regards studies on the acute effects on the *c* wave during drug administration the results are somewhat contradictory Junemann & Schulze (1968) found that intravenous and intraocular application of quinine and re sochin (a chloroquine derivative) resulted in a reversible selective pole inversion of the c wave in rabbits In contrast Hommer et al (1968) using narcotized cats found reversible changes from quinine but not from chloroquine There are several possible explanations for these result differences *i e.* the doses used the mode of administration the use of general anaesthesia etc It should also be emphasized that the recently discovered cyclic variations of the *c* wave (sheep Calissendorff et al 1974 man Skoog & Nilsson 1974) were not con sidered in these studies

The dual effect of chloroquine on the pigment epithelial layers and the neu roretina suggested by the present functional experiments is also indicated in some recent ultrastructural studies After acute retinal intoxication Berson (1970) and Smith & Berson (1971) reported changes mainly in the photoreceptor layer and Meier Ruge (1968) described swelling of the retinal pigment epi thelial cells with evidence of migration of pigment from these cells

To the author s knowledge the peculiar delayed reaction of the *c* wave after injection of small doses (less than 3 mg/kg b w of the drug) has not hitherto been described thus presenting an interesting problem It is tempting to attribute the delay to drug accumulation in the cells However if this were true one would expect slowly increasing changes of the *c* wave as the accumulation progressed whereas in this study the *c* wave changes appear rather suddenly Alternative explanations can be that either the toxic substance is a metabolite released after about an hour or that it takes some time for the accumulating drug to accomplish an effect in the cell activity strong enough to change the *c* wave of the ERG

As mentioned earlier the accumulation of the drugs in the pigment epithelial cells is considered by many investigators to be an important factor in the genesis of retinopathy The present study shows changes in the *c* wave amplitude and supports the view that the pigment epithelial cells are primarily involved How ever the immediate changes of the *b* wave after large doses of the drugs also indicate a direct neuroretinal toxicity

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MELANOTROPIC DRUGS AND RETINAL FUNCTIONS

II Effects of phenothiazine and rifampicin on the sheep ERG

BY

BERIT CALISSENDORFF

The acute effects of chlorpromazine, promethazine and rifampicin on the *a* *b* and *c* waves of the conventional electroretinogram (ERG) were studied in sheep Iv administration of chlorpromazine and promethazine resulted in a *b* wave amplitude decrease and an initial *c* wave amplitude decrease, followed by cyclic amplitude changes resembling damped oscillations Iv injections of rifampicin however resulted in cyclic changes of the *c* wave amplitude without initial concomitant *b* wave changes
The results of the present study indicate that rifampicin has a selective influence on the pigment epithelial cells while chlorpromazine and promethazine seem to have more generalized retinal effects on both the neuroretina and the pigment epithelial cells

Key words phenothiazine derivatives – chlorpromazine – promethazine – rifampicin – electroretinography – *c* wave – retina – pigment epithelium

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The existence of drug induced retinal lesions is well known in medical therapy although the pathogenesis of the side effects is not always clear In some cases absorption of the drug by the melanin containing choroid and the pigment epithelial cells probably plays an important role for the genesis of the retinal impairment In autoradiographic studies Potts (1962) demonstrated that melanin had a high binding capacity for polycyclic aromatic compounds Belonging to this group were the phenothiazine derivatives some of which are still in use as tranquillizers The accumulation of phenothiazine derivatives in the melanin containing tissues of the eye has since been confirmed in autoradiographic studies (Cassano et al 1968 Lindquist & Ullberg 1972 Lindquist 1973)

The phenothiazine derivatives were introduced in the early 1950s and the first report of retinotoxic side effects appeared in 1956 when Kinross Wright described severe vision impairment and pigmentary retinopathy following the use of piperidylchlorophenothiazine The retinotoxic effects of phenothiazine derivatives have since been confirmed in other clinical studies (Goar & Fletcher 1957 Siddall 1966 Kjaer 1968 Cameron et al 1972) as well as in experimental studies in cats (Meier Ruge & Cerletti 1966 Gregory et al 1970) Electrophysiological changes caused by phenothiazine derivatives have also been reported Henkes (1966) described pathological electrooculogram (EOG) and dark adaptation in patients treated with chlorpromazine Experimental studies in cats have shown acute reduction of the *b* wave of the ERG following administration of 10 to 20 mg/kg b w chlorpromazine while larger doses completely extinguished the *b* wave (Bornschein et al 1967) These findings point to a direct neuroretinotoxic action of the drug *but do not elucidate the possible role of the drug s melanin* affinity in the pathological process

Recently a new antibiotic substance rifampicin (3 (4 methyl 1 piperazinyl iminomethyl) rifamycin SV) used mainly as an antituberculous agent drug has been found to have melanin affinity (Boman 1973) Using a total body autoradiography technique marked radioactivity was found in the uveal tracts of pigmented mice after injection of ^{14}C labelled rifampicin Four days after the injection radioactivity was still present in the uveal tract and in the skin of the pigmented mice indicating a storage of rifampicin in melanin containing tissues Hitherto ocular side effects have not been observed in patients taking rifampicin but a preliminary communication indicates that the *c* wave of the sheep ERG undergoes amplitude changes after iv injection of large doses of this substance (Knave et al 1973)

Apart from the melanin affinity another common feature for both rifampicin and phenothiazine derivatives is the need for long term administration to obtain the desired therapeutic effect This may increase the risk of retinal side effects as a result of storage of the drug in melanin In the eye the melanin containing

tissue involved includes the uvea and the pigment epithelial cells of the retina. From experimental studies it is known that the activity of the pigment epithelial cells is reflected in the *c* wave of the ERG (Noell 1954 Brown & Wiesel 1961 Steinberg et al 1970 Schmidt & Steinberg 1971) This fact makes the study of the influence of melanotropic drugs on the *c* wave of especial import.

Recently an ERG method has been developed which allows long term d c registration and evaluation of the slow *c* wave from the intact sheep eye (Knave et al 1972 Calissendorff et al 1974) This technique has been used in the present work to study and compare the effect of iv administration of rifampicin and two melanin binding phenothiazine derivatives chlorpromazine and promethazine on the ERG Both phenothiazine derivatives are well known in clinical practice but retinal side effects have only been reported with chlorpromazine (Zelickson & Zeller 1964 Henkes 1966 Siddall 1965 1968)

Methods

The results were based on 12 experiments in which the ERGs were d c recorded from the intact eyes of dark adapted sheep A detailed description of the method has been given elsewhere (Knave et al 1972 Calissendorff 1976) Light stimulation was furnished by a Xenon arc lamp (Zeiss 900 W) The intensity of the light flashes was 4.5–5 0 log units above the *b* wave threshold which allowed a proper evaluation of the *a*- *b*- and *c* waves The duration of the flashes was 1 0 sec and the stimulus interval 30 sec The amplitude values were calculated from the means of two consecutive summated responses The amplitudes of the *a* and *c* waves were measured from the isoelectric line and the *b* wave from the trough of the *a* wave

After 3 h of dark adaptation the sheep eye was intermittently stimulated with a frequency of 2/min for 100 minutes After this time a constant level of the *c* wave amplitude was reached (Calissendorff et al 1974) and the various drugs were administered

The drugs tested were injection solutions of chlorpromazine (Hibernal® 10 (3 dimethylaminopropyl) 2 chlorophenothiazine) promethazine (Lergigan® 10 (2 dimethylaminopropyl)phenothiazine) and rifampicin (3 (4 methyl 1 piperazinyl iminomethyl rifampicin SV) The drugs were diluted in 50 ml Ringer solution and slowly administered iv Chlorpromazine was administered in single doses of 1 and 10 mg and rifampicin was used in three different concentrations (1 mg 5 mg and 10 mg/kg b w)

Results

In the present experimental series the effects on the d c recorded ERG after iv administration of three different drugs with melanin affinity were studied The three drugs used were chlorpromazine (5 experiments single doses from 1 mg to 50 mg) promethazine (2 experiments single doses 10 mg and 100 mg) and rifampicin (5 experiments doses of different concentrations 1 mg 5 mg and 10 mg/kg b w) it should be mentioned that these doses roughly correspond to those used in clinical practice

Phenothiazine derivatives

In Fig 1 the amplitudes of the *a* *b*- and *c* waves are graphically illustrated from an experiment in which 1 mg and later 10 mg chlorpromazine were injected (arrows) Only minutes after the first iv injection (1 mg) the *b* and *c* wave am *plitudes decreased about 50 μV The b wave slowly recovered and after about*

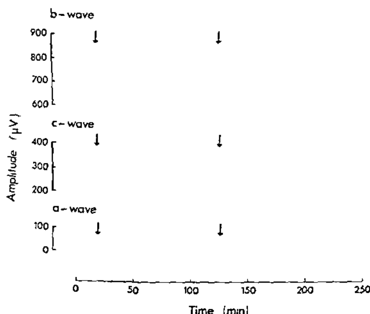


Fig 1

Effects of chlorpromazine on the *a* *b* and *c* wave amplitudes of the dark adapted sheep eye After 20 min (arrows) and 125 min (arrows) 1 and 10 mg chlorpromazine respectively were injected intravenously Stimulus intensity 5 0 log units above *b* wave threshold Stimulus duration 1 sec

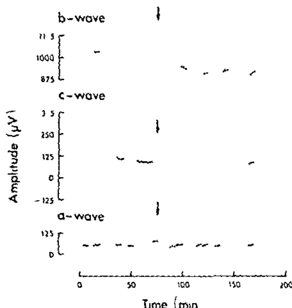


Fig 9

Effects of a single iv injection of 100 mg promethazine (arrows) on the *a*, *b* and *c* wave amplitudes of the dark adapted sheep eye. Stimulus intensity 4.5 log units above *b* wave threshold. Stimulus duration 1 sec

100 min the original amplitude level was reached. The *c* wave regained amplitude about 5 min after the initial decrease whereupon its amplitude underwent oscillatory changes. No changes in the *a* wave were observed. The administration of the larger dose (10 mg at 130 min) of chlorpromazine resulted in amplitude changes of principally the same type but of greater magnitude. Here the initial depression of the *b* wave amounted to about 200 μV and the recovery was not yet complete after 3 hours observation. The *c* wave changed in amplitude with a damped oscillation pattern.

Fig 2 shows the amplitudes of the *a*-, *b* and *c* waves after slow iv injection of 100 mg promethazine in 50 ml Ringer solution (arrow). The injection resulted in a depression of the *b* wave amplitude. The decrease was complete after about 30 min and amounted to about 150 μV. The depression of the *b* wave amplitude persisted during the entire time of the following registration. The *c* wave amplitude rapidly decreased about 150 μV. This decrease began immediately after the administration of the drug and was followed by an increase more than 200 μV larger than the initial base level of the *c* wave amplitude. This large initial peak was followed by another smaller peak 30 min later the

c wave amplitude then seemed to reach a more or less constant level of about 100 μV

No significant changes in the *a* wave amplitude were observed it remained at a level of about 50 μV throughout the experiment. The small dose (10 mg) resulted in amplitude changes in the *b* and *c* waves which were basically of the same type but of a lesser magnitude. A tendency towards slow recovery was observed in the *b* wave amplitude

Besides the afore mentioned effects large doses of the drugs lowered the *blood pressure however this reduction was less than the blood pressure re*duction produced by vagal nerve stimulation which has been shown to have no influence on the sheep ERG (Knave & Persson 1973)

Rifampicin

Fig 3 shows the effects from a single iv injection of 5 mg/kg b w rifampicin (arrow) The *a* wave amplitude remained constant The *b* wave amplitude slowly increased simultaneously a slow increase of the *c* wave amplitude was

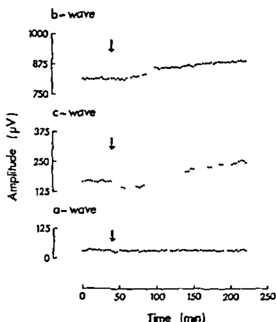


Fig 3
Effects of a single iv injection of 5 mg/kg b w rifampicin (arrows) on the *a* *b* and *c* wave amplitudes of the dark adapted sheep eye Stimulus intensity 4.5 log units above *b* wave threshold Stimulus duration 1 sec

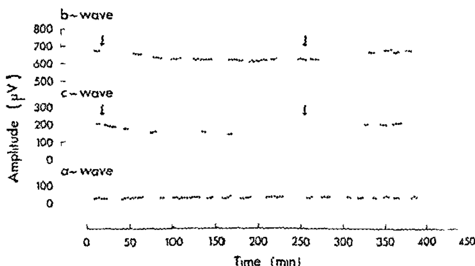


Fig 4

Effects of rifampicin on the *a* *b* and *c* wave amplitudes of the dark adapted sheep eye After 20 min (arrows) and 250 min (arrows) 1 and 10 mg/kg b w rifampicin respectively were injected intravenously Stimulus intensity 4 5 log units above *b* wave threshold Stimulus duration 1 sec

observed The *c* wave amplitude also exhibited cyclic variations beginning immediately after drug administration Following a rapid decrease the *c* wave started to oscillate with a frequency of 2–3/h

Fig 4 shows the results of an experiment in which the *a* *b* and *c* waves were followed for 450 min after the constant *c* wave amplitude level had been reached After 20 and 250 min two single doses of rifampicin (1 and 10 mg/kg b w respectively) were given (see arrows in the diagram) No effect was observed in the *a* wave amplitude Nor was any change found in the *b* wave amplitude with the exception of a very slow temporary decrease concomitant with a similar slow decrease in the *c* wave amplitude No immediate changes in the *c* wave amplitude were observed but in time a tendency towards oscillatory variations appeared After about 100 min these oscillatory changes slowly subsided Following the second injection (10 mg/kg b w) the oscillatory pattern of the *c* wave changes was more prominent

The oscillatory variations had a frequency of 2–3/h and increased in amplitude towards the end of the experiment to a maximum of 125–150 μV In addi

tion to these rather rapid changes in the *c* wave amplitude a slow decrease in the mean level was observed during the two hours following the first injection The decrease was followed by a slow increase in the course of the next two hours the increase being almost completed at the time of the second injection. Blood pressure or heart rate changes related to the rifampicin inject ons were not observed Administration of the solution without rifampicin did not result in any ERG changes

Discussion

Iv injections of chlorpromazine and promethazine caused changes in both the *b* and *c* wave amplitudes Both drugs affected the ERG in the same manner the changes were dose related and significantly small doses influenced both the *b* and *c* wave amplitudes Contrary to the phenothiazines rifampicin was found to have an effect mainly on the *c* wave This effect was dose related and could be seen even with doses comparable to those used in rifampicin treated humans

The effect of phenothiazine derivatives on both the *b* and *c* wave amplitudes points to a dual site of action the *b* wave reduction presumably arising from a toxic action on the neuronal structures in the inner nuclear layer and the *c* wave changes indicating an involvement of the pigment epithelial layer This assumption is supported by other studies Ulrich & Wundsch (unpublished see Wundsch & Ulrich 1972) used large doses of chlorpromazine to extinguish the *b* wave of the ERG in cats and Bornschein et al (1967) showed that the drug s effect on the *b* wave was dose dependent There are also studies indicating influence on the pigment epithelial cells Alkemade (1968) found pathologic clinical electrooculograms in 9 out of 13 patients with phenothiazine induced retinopathy In cats the pigmentation of the retina was associated with accumulation of lipids in the pigment epithelium and preceded by destruction of peripheral rod segments (Meier Ruge & Cerletti 1966) It should also be pointed out that chlorpromazine is reported to be absorbed and concentrated by pigment granules in the uvea (Potts 1962 Green & Ellison 1966 Meier Ruge et al 1966 Cassano et al 1968) As the pigment epithelial cells contain melanin it seems reasonable to suppose that an accumulation of the drug in the pigment epithelial cells of the retina takes place However the effect on the pigment epithelium indicated by the *c* wave changes in the present study occurs too quickly to represent a manifestation of drug accumulation it points more to a direct in

fluence on these cells As no isolated effects on the *c* wave were recorded in the present study it is difficult to say whether the effects on the neuroretina and the pigment epithelium occurred separately or whether one reaction induced the other

As for rifampicin the selective initial changes in the c wave occurring only minutes after injection indicate a direct influence on the pigment epithelial cells In contrast after administration of the small dose (1 mg/kg b w) (Fig 3) the *c*-wave changes are not clearly visible until after about 1 h A possible explanation is that the initial concentration of rifampicin in the pigment epithelial cells is not high enough to elicit any immediate *c* wave change but that by a process of accumulation such a level will subsequently be reached Drug accumulation in the pigment epithelial layer would also explain the observed cyclic variations which were still increasing more than 3 h after a single injection of 10 mg/kg b w (Fig 4) According to Boman (1973) a marked radio activity in the uveal tract can be observed a few hours after iv injection of ^{14}C labelled rifampicin in mice This fact may lend support to the idea that drug accumulation engender the observed *c* wave variations

No certain relationship was found between the slow variations of the *b* and *c* waves and the administration of rifampicin Thus the slight slow decrease of the *b* and *c* waves observed after the first injection (Fig 4) was followed by an increase which had begun before the second second injection Furthermore these slow changes were not a constant finding as apposed to the faster oscillations of the *c* wave invariably observed after injection of rifampicin These slow changes might be part of the recently described slow cyclic variation of the c wave amplitude (Calissendorff et al 1974) or effects of a more general origin e g temperature of the electrodes (Ives & Janz 1969 Skoog 1974) The small rapid oscillations of the *b* wave observed after injection of 10 mg/kg b w probably represent subordinate effects from the *c* wave amplitude changes as the *b* wave is partly superimposed on the *c* wave

The results of the present study indicate that small doses of rifampicin and phenothiazine differ to some extent in their effects on the ERG Although both drugs have melanin affinity only rifampicin was found to have a direct immediate influence on the *c* wave which is known to reflect the activity of the pigment epithelial layer The phenothiazine effects on the *c* wave amplitude were complicated by simultaneous effects on the *b* wave amplitude Selective *c* wave changes were not obtained even using small doses of the drugs A similar generalized effect on the sheep ERG can also be seen with barbiturates and alcohol (Knave et al 1974a b) which like phenothiazine affect the central nervous system Thus phenothiazine seems to have a complicated neuroretinal influence with immediate effects on both the pigment epithelial cells and the neuroretina

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The etiology of progressive retinal cone dystrophy is still obscure but it is probably heterogenous (Goodman et al 1966 François et al 1974 Ohba 1974) In a group of patients developing cone dystrophy we have found disorders of different organ systems suggesting that one type of cone dystrophy may be an ocular manifestation of a systemic disease The purpose of the present paper is to report the ocular findings and visual performance of the patients with this disorder

Patients

Seven patients 6 females and 1 male were studied Their ages at the first examination varied between 6 and 41 years The length of observation time varied between 1 and 8 years Patients 1 2 and 3 were sisters and cousins of cases 4 5 and 6 These patients all females belong to a highly inbred kindred Patient no 7 belonged to a different family and he had had an older brother who had died at the age of 6 months and who may have had the disease

Patient 1 (G S) who was 23 years of age had always had poor vision and photophobia At school she could read her books at close distance, finally with magnifying glasses The reading improved in twilight At the age of 19 years her visual acuity was reduced to finger counting at 4 m in each eye The vision had decreased considerably during the year prior to admission and at the same time the photophobia had become more pronounced The patient had been able to distinguish some colours at school but her colour vision totally disappeared some years later The findings at our examination were nystagmus of pendular type slight coerulear cataract pallor of the optic discs and attenuated retinal vessels No pigment deposits could be seen some faintly greyish spots were noted in periphery of the left fundus The macular contours were diffuse The visual acuity was finger counting 1 m with the right eye and light perception 1½ m with the left eye During the observation period of 16 months the visual acuity became further reduced to finger counting about at 20 cm in the right eye with amaurosis in the left eye

Patient 2 (G N) female, 20 years of age had been operated on because of esotropia at the age of 6 and the visual acuity was then 6/12 in each eye Her vision had decreased during the last 6–7 years and photophobia had been present for the same length of time In cloudy weather and in twilight she could see better than in daylight. Although she had always been unable to distinguish between blue and green her colour perception had been better at school than in the later years and it was eventually completely lost

Examination revealed a course pendular nystagmus She had a slight alternating exotropia with poor fixation The pupils reacted slowly to light Some blurring pallor and slight prominence of the optic discs were found The macular pattern was not distinct and there was no foveolar reflex The retinal vessels were narrow No pigmentation could be seen The visual acuity was 5/60 in each eye and remained constant during the observation period.

Patient 3 (K N) was first examined at the age of 11 when we examined other family members She denied any visual disturbances Closer examination revealed that bright daylight was discomforting to her and she preferred to stay in the shadows and dark places At the school examination at 7 years of age the visual acuity had been 5/5 in each eye When she was 10–11 years of age her mother had noticed that she experienced difficulty in seeing the yellow orange colour of cloudberries in their natural surroundings She exhibited a slight photophobia Ophthalmoscopy was normal but no clear foveolar reflex could be seen At the first examination visual acuity was 6/8 5 in the right eye and 6/7 5 in the left eye A slight reduction to 6/10 in each eye was registered during the observation period (28 months)

Patient 4 (G Å) has not been examined by us She died from meningitis in 1972 at the age of 44 Reading vision had been present when she was a child There had been deterioration of vision quite parallel to that of her sisters She had an attack of apoplexia in 196? and was then examined by an ophthalmologist who found pallor of the optic discs and narrow retinal arteries together with some hypertensive changes The visual fields were normal and the visual acuity was 1/30 in the right eye and 1/?0 in the left eye. The following year a large scotoma in the inferior and temporal part of the left visual field was recorded By 1970 the vision was reduced to light perception in each eye

Patient 5 (O I) 41 years of age had been partially sighted from childhood Her photophobia was already noticeable at school age and she could remember that she was able to see red whortleberries only after sunset The colour vision had decreased from the age of 7 years

Operation was performed in the neurosurgical department following a sudden loss of vision at the age of 40 years An empty sella syndrome was diagnosed (Hauge & Froyshov Larsen) Post operatively her vision gradually returned over a period of 4 months An irregular pendular nystagmus was recorded The pupils reacted slowly to light A slight pallor of the optic discs was found and the retinal vessels were thin The fundus had an atrophic appearance but no pigmentation was recorded The macular pattern was diffuse. The visual acuity was 6 60 in the right eye and 4/60 in the left eye and it did not decrease during a ?0 month period of observation There were central scotomas and restricted visual fields in the lower left quadrants

Patient 6 (K A) 40 years of age remembered that she could see well at the age of 6 years but that vision had decreased gradually during the school years Bright light had been poorly tolerated from the age of 10 years and the visual performance became worse in daylight and was relatively best in twilight She had had no problems with colours during the first years at school From the age of 10 years she began confusing green and blue later on brown, violet and black and eventually no colours at all could be distinguished From the age of 19 years her vision had been stationary

The pupils reacted well to light There was no nystagmus Some pallor of the optic discs and narrow retinal vessels were seen The maculae appeared diffuse There was no pigmentation apart from a single p gmented spot peripherally in the right fundus The visual acuity was 6/36 in each eye and it was improv d to 6 4 in subdued ligh

Patient (I H) a boy aged 6 years at the time of the first exam nation Delivery had been complicated and the boy was mentally retarded He is a d zygo c tw n His twin brother is normally sighted and has good colour vision There was no known consan

guinity and no other cases of the same disease in the family From the age of 5 years it had been evident that the patient s vision was poor He was bothered by daylight and preferred the dim light in the evening There was photophobia and irregular nystagmus of pendular type. The pupils reacted slowly to light There was a general atrophic appearance of the fundi and a feeble demarcation of the maculae. The optic discs had a slight greyish appearance and the retinal vessels were narrow Visual performance gradually declined. At the age of 7 years he could read his school books with difficulty and could name some colours The visual acuity was 4/60 in each eye. At the age of 14 years he had changed to reading Braille and the visual acuity was 1 5 60 in the right eye and less than 1/60 in the left eye The right visual field was slightly restricted and only the temporal lower field was preserved on the left side

Studies on the Patients Vision

Perimetry examination with the Goldmann perimeter was performed in the usual way as dynamic and static perimetry and was supplemented by examination under scotopic conditions The central as well as the peripheral functions were further analyzed by measuring increment thresholds of colour stimuli during chromatic adaptation using a method which has been previously described (Hansen 1974b)

Dark adaptation was registered with a Goldmann Weeker s adaptometer after a preadaptation period of 5 min at 2400 lx Integral adaptation was used in one patient With an average technique electro retinography (ERG) responses to single flash and flicker stimuli were recorded in 3 patients and in 1 patient with single flash alone Visually evoked response (VER) was performed in 2

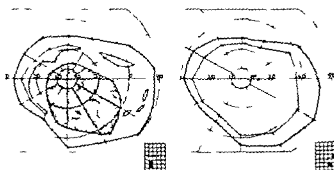


Fig 1
The right visual field of case 1 recorded under standard conditions (31 5 asb) (on the left in the figure) and under mesopic conditions (0 315 asb) (on the right in the figure)

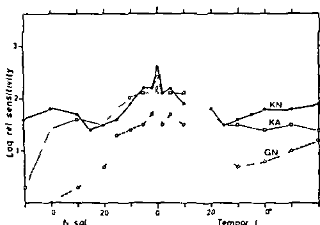


Fig 2

Static perimetry recorded with standard illumination (31 5 asb) in case 2 (GN) case 3 (KN) and case 6 (KA) The shaded area indicates the variation (mean ± 2 SD) of 5 normal persons Object size IV (16 mm²)

patients and fluorescein angiography in 2 patients The pulse synchroneous variations in intraocular pressure were registered in 5 patients by dynamic tonometry using a method described by Hørven (1970)

The colour vision tests were administered under two *Macbeth Illuminant* C lamps The following tests were used The AO H R R and the Ishihara pseudo isochromatic plates (11th ed) the Farnworth s tritan chart, the tissue paper contrast charts of the Velhagen Stilling test (21st ed) and the Cohn s test (1905) the Umazume Ohta scotometric plates (Ohta 1972) and the Sloan s achromatic test (Sloan 1954) A series of charts reproduced from the Ishihara test in black and white shades were shown parallel with the pseudo isochromatic tests (described by Hansen 1963) All the patients were examined with the Farnsworth s D 15 test and patient no 3 also with the Farnsworth s 100 Hue test Anomaloscopic examinations were performed with a Nagel anomaloscope type I

Perimetry data

With large and clear objects normal limits were registered in cases 1 2 3 and 6 A large central scotoma was found in case 1 and could also be demonstrated in the other patients with objects of less intensity (II/2 in case 2 I/2 in case 3 and IV/2 in case 6) Under mesopic conditions no central scotomas were present

(Fig 1) With static perimetry there was a marked decrease in threshold sensitivity especially within 30° of eccentricity (Fig 2) Static perimetry performed during total dark adaptation showed a clearly better threshold sensitivity in relation to the normal level (Fig 3)

Colour vision

The F D 15 test was the most easily performed test and showed grave confusion of colours scotopic pattern was demonstrated in cases 2 5 and 6 Only in case 3 was the test performed correctly However with the 100 Hue test she had a high error score without predominant axis (Fig 4) This patient could read the most saturated figures in the AO H R R test intended for red green and blue yellow defectives but missed the other charts and the greater part of the Ishihara test She could not read the tissue paper contrast tests with blue green and red purple backgrounds Except for some occasional charts all the other patients missed the AO H R R test and the Ishihara test The Farnsworth s tritan test could not be performed by patient 2 while patients 3 and 6 could see the green but not the blue square Patient 3 indicated a brighter colour in the centre than in the periphery with the Okazuma Ohta test on chart 3 (red purple) and 5 (green)

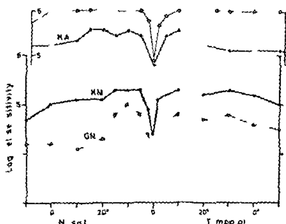


Fig 3

Static perimetry under scotopic conditions recorded with near monochromatic object light (λ_{max} = 515 nm) The shaded area indicates the variation (mean ± 2 SD) of 5 normal subjects Object size III (4 mm²) Case 6 (KA) was examined with object IV (16 mm²) and the corresponding values for a normal person is indicated by dashed lines (top)

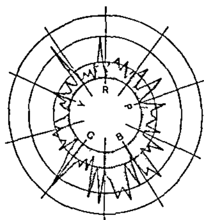


Fig 4

Performance of the 100 Hue test by patients 3 at the age of 13 years
Total error score 282 (as against 192 one year previously)

A series of charts in black and white shades could easily be seen by patients 3 and 6 (except for 1 chart) and by case 2 in about half the number Sloan's test for achromats could be performed well by patients 2 5 and 6 while the statements of patient 1 were unprecise (Fig 5) Matches could not be obtained by patient 3 who could instead obtain perfect matches in the anomaloscope

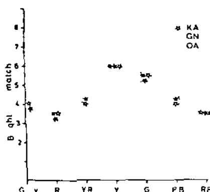


Fig 5

Performance with the Sloan's achromatic test by 4 patients The dashed vertical lines indicate the uncertainty of the matches of case 1 The shaded area indicates the variation (mean ± 2 SD) of 1[illegible] achromats according to Sloan (1954)

Table I

The performance of 4 patients in the Nagel anomaloscope expressed by the yellow values used to match the upper field (the red green values)

Case	Red green value							
	73	70	65	60	50	40	30	0
1	*0*			*20–35*		*70 to max*		*Not possible*
2	1			23–25	4?–45½	62½–63	81–84	Not possible
5	1	*5*	15	25½		*52*	*78*	*Not possible*
6	1	3½		25½–27½		68–69		Not possible

Case 3 had normal settings 44½–45½/16 (anomalous quotient = 0 76)

within the normal range As is seen from Table I the other patients could obtain *matches all over the scale except in the green end (value 0) Particularly dark* values were obtained for the red light (value 73) The settings were typical achromatic Case 7 had unprecise settings but stated that red was very dark and green too bright for matching

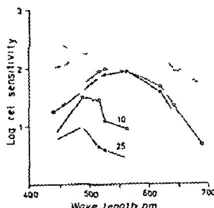


Fig 6

Relative spectral sensitivity recorded against the neutral background (31 5 asb) in case 3 at the age of 13 years by central localization and at two positions in the temporal field The dashed line indicates the central recording 1 year previously Shaded area indicates the variation (mean ± 2 SD) for 5 normals

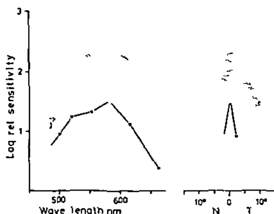


Fig 7
Relative spectral sensitivity recorded centrally in case 3 during adaptation to blue light (Wratten 47 165 lx) and static perimetry performed against the same background with monochromatic object light (λ_m = 582 nm) Shaded area indicates the normal variation (mean ± 1 SD)

Spectral sensitivity during adaption to white and coloured back-grounds

The spectral sensitivity curves obtained against neutral background for case 3 did not differ much from the normal shape but the level was lowered by about ½ Log unit in relation to that of the normal (Fig 6) At the perimetric angles 10 and 25° the spectral sensitivity curves were essentially changed with a maximum now localized at about 500 nm In the blue and purple adapting colours the response patterns indicate the presence of red and green sensitive receptors centrally however with a very rapid decline in peripheral direction (Figs 7 and 8) No blue receptor response could be elicited in the yellow back ground light when these examinations were performed at the age of 13 years

In case 2 and 6 only one type of response pattern could be produced irrespective of the background colours i e with maximal spectral sensitivity being about 500 nm (Fig 9) In case 1 only subdued white blue and yellow back ground lights could be used Maximal sensitivity was likewise obtained at about 500 nm

Dark adaptation

In case 3 the dark adaptation curve was biphasic with a weak first phase The final threshold level after 25 min was stabilized at about 5 Log unit below the

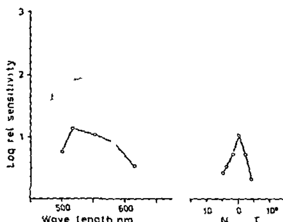


Fig 8

Relative spectral sensitivity recorded centrally in case 3 with a purple background (Wratten 34A 200 lx) and static perimetry performed against the same background with monochromatic object light (λ_{max} - 552 nm) Shaded area indicates the normal variation (mean ± 1 SD)

starting level For cases 1 2 5 and 6 there were monophasic curves which stabilized at about 4 Log unit (Case 1) and 4½ Log unit (Cases 2 5 and 6) below the starting level after 25 min

Electro retinography

Electro retinography was performed in case 1 with single flash stimuli of high intensity which produced a good response though with lack of first wavelet. No response was present for single flash red light A reduced response was found

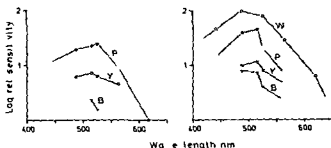


Fig 9

Relative spectral sensitivity recorded in case 2 (left) and case 6 (right) during adaptation to standard white (W) purple (P) yellow (Y) and blue (B) background lights

with the summation method performed in case 2 using single flash stimuli. Flicker response at 25 Hz was only minimal and was absent at 50 Hz. Patient 6 had quite a good response to single flash stimuli under scotopic conditions. In room illumination there was a very weak flicker response at 20 Hz and 40 Hz. Patient 3 had quite a good response to single flash stimuli and slow flicker at 10 Hz. Clear and distinct responses though with reduced amplitudes were also found to flicker stimuli at 50 Hz.

Dynamic tonometry

Low corneal indentation pulse amplitudes were found in all the patients examined (cases 1, 2, 3, 5 and 6). Their average value was 14.1 μ (s.d. = 3.53). As compared with the average value found in normal persons below the age of 60 years in Hørven's material (1970), i.e. 31.48 μ (s.d. = 10.79), there is a significantly reduced level of pulse amplitudes in our patients (Student's *t* test, t = 3.57, $P < 0.01$).

Other examinations

Fluorescein angiography was performed in cases 2 and 3 and was normal.

VER in the least affected patient (case 3) demonstrated a normal single flash evoked response after a normal latency period. For patient 2, no response could be registered to single flash stimuli in ordinary room illumination nor to slow flickering stimuli at 10 Hz. However, under mainly scotopic conditions a clear single flash evoked response was seen after a normal latency period.

Metabolic Studies

Detailed metabolic and clinical studies will be reported elsewhere. In this paper a concentrate of the metabolic data (Table II) is presented. Two patients had repeated abortions, two were probably infertile. The boy (case 7) had hypogonadism. In spite of the menopause there was no elevation of luteinizing hormone (LH) in case 6. The response to gonadotropin releasing hormone (LHRH) was normal in three and low in two patients. A defect in the ACTH reserve as tested by Metyrapone® was found in two patients, in the growth hormone secretion in another two patients (tested by insulin induced hypoglycemi) and in the thyroid function in two patients.

Three of the patients had diabetes (two of them were obese) and a fourth patient had a pathological glucose tolerance (and was obese).

Table II

Some clinical and metabolic observations in 7 patients with progressive cone dystrophy

Case	Sex	Age (years)	Clinical endocrine problem	Obesity	Glucose tolerance	Gonadal pituitary function	Suprarenal pituitary function	Thyroid pituitary function	Growth hormone	Liver disease	Hearing defect
1	F	24	2 abortions amenorrhoea	+	P*	N	N	N	P?	+	+
2	F	21	–	+	P	N	N	N	P	+	(+)
3	F	17	–	–	N	N	N?	N	N	–	–
4	F	44	9 abortions	+	P*	NE	NE	P	NE	NE	+
5	F	43	Infertility?	–	P*	P	N	N	NE	NE	+
6	F	40	Infertility?	–	N	LN	P	N	N	+	+
7	M	11	Small testes	+	N	P	P	P	NE	+	+
No with trait/total no			5/7	4/7	4/7	2(3?)/6	2/6	2/7	2?/4	4/5	5(6?)/7

F Female M Male P Pathologic values N Normal values NE Not examined LN Low normal P* Manifest diabetes

Liver biopsies were carried out in four patients due to slightly elevated transaminase (SGPT and CPK) values Pathological changes were found in all of them. The degenerative liver disorder observed will be discussed in a separate paper

Discussion

There are few reports on the association of progressive cone dystrophy with signs of systemic disorders Bjørk et al (1956) presented five cases with progressive cone dystrophy in association with hereditary ataxia of Pierre Marie s type Siegel & Smith (1967) described a patient who developed a generalized cone dysfunction following therapy for a systemic infection complicating a ce arean section Walsh & Hoyt (1969) reported a case with selective and progressive involvement of the retinal cones associated with an unexplained disease of the central nervous system One of the cases of Babel & Stangos (1973) belonged to a family with a prevalence of multiple sclerosis Berson et al (1968) described a case of polydactyly and obesity in one of their patients with combined cone rod degeneration Franceschetti et al (1963) reported a boy with absent cone function and reduced rod function associated with polydactyly hypogenitalism and obesity On the basis of this Berson et al suggest that their case of cone rod dystrophy is a forme fruste of the Laurence Moon Biedl syndrome Another patient seen by us with a cone rod dystrophy (described as case 2 in the report by Hansen (1974a)) had polydactyly Her sexual functions were normal However after pregnancy and childbirth there was a marked deterioration of vision

In this series of patients severe impairment of vision was seen in case 1 when she was about 20 years of age and had had two spontaneous abortions Case 4 had had 9 abortions and there was an almost total loss of vision by the age of 42 years Impairment of vision concommitant with pregnancy in patients with cone dystrophy has been described in two cases by Steinmetz et al (1956) and in one case mentioned by Fite (1968) However in our patients there had been no childbirths and a certain degree of hypogonadism was recorded

Our patients have a general appearance of early ageing and several pathological traits apart from the ophthalmological ones reported here There were endocrinological disturbances affecting different organs pathologic glucose tolerance distinct signs of liver disease and hearing defects of cochlear type Apparently the progressive cone dystrophy is part of a disease which affects many organs There is no evidence for exposition to toxic agents The familial occurrence of the disease suggests that it is inherited and genetic studies will be reported in a separate paper

The characteristic ophthalmological feature exhibited by our patients is the loss of function of the photopic mechanism Photophobia was present in all the patients and had developed simultaneously with the reduction of vision The visual performance was said to be clearly better in twilight than in daylight and in two of the patients (cases 2 and 6) improvement of the visual acuity in reduced illumination could be demonstrated Particular diagnostic importance has been attached to this sign (Zweifach & Wolf 1968 Ohba 1974)

There was a striking disappearance of the central scotomas when the illumina tion was changed from photopic to mesopic conditions and this was particularly pronounced in patient 1 There was an unquestionable scotopic pattern demon strable by the anomaloscope settings by the Farnsworth s D 15 test and the Sloan s achromatic test The spectral sensitivity measurements in these patients demonstrate only one type of receptor function i e the rhodopsin pattern independent of the variations of the adapting field As is shown by the static perimetry during dark adaptation there is also some affection of the scotopic mechanism Therefore a combination of cone and rod dystrophy is present with however a preponderance of the cone defect Krill & Deutman (1972) pointed out that the rod mechanism may eventually become involved to a varying degree in cone dystrophies and that it is therefore meaningsless to draw a sharp distinc tion between pure cone dystrophies and cone rod dystrophies Our observations support this view

The least affected patient (case 3) is particularly interesting since she probably exhibits the disease process at a very early stage In spite of poor performance with the pseudo isochromatic charts the tissue paper contrast tests and the 100 Hue test her performance with the clear spectral colours of the anoma loscope was very good The presence of the red and green receptor mechanisms was confirmed by the chromatic adaptation studies However their sensitivity level was reduced and they could only be traced in a very limited central part of the visual field whereas the more peripheral recordings showed a scotopic pattern Therefore in respect of the cones a true tube vision was demon strated By using flicker examinations Fourtes et al (1961) likewise found functioning cone vision in only a restricted central area in an incomplete achro mat The diagnostic value of ERG was stressed by Kelsey & Arden (1972) As our case 3 had a reduced but clear cone response with the flicker ERG her cone population must be reduced in number rather than in quality François et al (1974) found with the summation method that there is a gradual reduction of the ERG response

In all our advanced cases the fundus picture was quite similar with a general atrophic appearance absence of pigmentation and no clear demarcation of the macula Attenuated vessels and disc pallor were characteristic findings in our

patients apparently distinguishing them from most cases of cone dystrophy However Bjork et al (1956) described attenuated vessels and disc pallor and Sloan & Brown (1962) described a case with temporal pallor of the disc Krill & Deutman (1972) found normal vessels as well as slightly attenuated vessels The fluorescein angiography performed in two patients was normal as in the cases reported by Ohba (1974) and by François (1974) This finding is consistent with a primary degeneration of the neuroepithelium as suggested by Ohba Pathologic changes in the angiogram were described by Yokoyama et al (1973) and by Babel & Stangos (1973) The narrow retinal vessels and the disc pallor observed in our patients suggest extensive involvement

The results obtained by dynamic tonometry indicate a reduced choroidal circulation (Horven 1973) It is interesting to note that low pulse amplitudes are not a characteristic finding in the typical total achromats of stationary type (personal observation) but are a typical finding in the pigmentary dystrophies (Horven 1970) In this particular type of cone dystrophy the process is evidently just as extensive as in the pigmentary dystrophies

Acknowledgments

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ELECTROPHYSIOLOGICAL AND ANATOMICAL EFFECTS OF CETYLPYRIDINIUM CHLORIDE ON THE RABBIT CORNEA

BY

KEITH GREEN

The effects of cetylpyridinium chloride on the trans corneal potential difference and the surface anatomy of the cornea have been examined Concentrations of cetylpyridinium chloride from 0 21 mM to 2 mM were used for either 1 or 2 minute exposure times on the *in vitro* and *in vivo* cornea for the electrophysiology studies The potential difference of the *in vitro* cornea showed a concentration and exposure time dependent de crease, the *in vivo* cornea shows a qualitatively similar behaviour although quantitatively less The fall in potential difference is preceeded by a hyper polarization. The scanning electromicroscopy reveals a loss of microvilli and microplicae as well as surface pitting with some exposure of cells underlying the superficial epithelium. These changes occur in a dose de pendent manner The effect of cetylpyridinium chloride on the cornea is to enhance the permeability of the superficial cells by destroying the cell membranes and causing lysis of the cells

Key words cetylpyridinium chloride – cationic surfactant – rabbit – cornea – scanning electron microscopy – electropotential

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In 1971 Green & Tonjum described the effects of various agents including two cationic surfactants (benzalkonium chloride (BA) and cetylpyridinium chloride (CPC)) on corneal permeability to fluorescein It was found that both agents caused a marked increase in permeability in conjunction with a lysis of the outermost cell membranes indeed the effects of CPC at 2 mM were most pronounced but only one concentration of CPC was employed

Recently some studies on drug penetration into the eye have examined the relationship between drug protein interaction in the tear film and the effect of CPC on releasing adsorbed drug from tear film proteins following drug instillation onto the eye (Mikkelson Chrai & Robinson 1973) These authors suggested that the 10 fold increase in biological activity of pilocarpine in the presence of CPC was the result of competitive inhibition of drug protein interaction causing release of adsorbed drug The concentration of CPC used was 0 56 mM (0 02 %) compared to the 2 mM used by Green & Tonjum (1971) and it was suggested (Mikkelson Chrai & Robinson 1973) that the concentration difference together with the difference in technique was responsible for the alternative interpretation of CPC effects Other studies (Smolen Park & Williams 1975) have indicated that drug penetration depends on the fixed charges both within and upon the cornea and that substances such as benzalkonium chloride affect drug binding sites on the corneal surface

In order to fully investigate the effect of CPC on the cornea both electrophysiological and anatomical studies were performed on both *in vivo* and *in vitro* rabbit corneas

Materials and Methods

Adult healthy albino rabbits 2–4 kg of either sex were used

Electrophysiology The procedures for both *in vitro* and *in vivo* determinations of corneal potential followed those given previously (Green & Tonjum 1975) Corneas were mounted in chambers which allowed a 15 mmHg hydrostatic pressure to be maintained on the posterior surface The chamber was immersed in a beaker containing sufficient Krebs bicarbonate Ringer with glucose at 5 mg/ml (pH 7 4) to cover the exposed corneal surface The potential difference (PD) was measured with a Heath EU 20B recorder to an accuracy of ± 0 1 mV

Experiments were made with normal Ringer initially on both sides of the cornea After 10 to 15 min all tissues exhibited a stable PD An identical Ringer solution containing either 0 21 (0 075 mg/ml) 0 56 (0 2 mg/ml) or 2 mM (0 716 mg/ml) cetylpyridinium chloride (CPC) was placed in another beaker

and the chamber placed in this solution for either 1 or 2 min The exposed surface of the cornea and the chamber was washed with at least 200 ml of normal Ringer before reimmersion in a beaker containing Ringer alone One series of experiments followed the ensuing steps in Ringer until the PD was stable into a solution of 2 % pilocarpine hydrochloride and 100 mg % bovine serum albumin again until a stable PD was reached (less than 3 min) then exposure for 1 min to a pilocarpine albumin solution containing 0 56 mM CPC followed by a washing phase and return to normal Ringer The trans corneal PD was measured during all phases except the washing phase At least 4 corneas were used at each concentration and exposure time

In vivo experiments were also performed in a manner identical to that described previously (Green & Tonjum 1975) except that CPC at 0 56 mM or 2 mM was utilized in the corneal cup The exposure time to either concentration was either 1 or 2 min

Anatomy All three concentrations of CPC were used in the *in vivo* situation in the following regimens 3 drops with each drop every 30 seconds and 10 drops each applied every 30 seconds Control corneas received 10 drops of 0 9 % saline solution 1 drop every 30 seconds Fifty microliter drops were applied to each cornea The corneas were quickly removed from the eye and immersed in 3 % glutaraldehyde The fixed corneas were then prepared for scanning electron microscopy and examined at Mid America Microanalysis Lab Inc where the microscope operator was not aware which specimen was under examination

Results

Electrophysiology Cetylpyridinium chloride (CPC) at all concentrations and exposure times examined both *in vivo* and *in vitro* caused an initial hyper polarization of the potential difference (PD) within 12 to 20 seconds after ex posure The PD then fell rapidly in a concentration dependent manner to a minimum (Table I) Generally longer exposure times caused greater falls in PD The recovery rate of PD to normal pre treatment levels was also exposure time and concentration dependent (Table I)

In vitro experiments Normal values of PD for the different experimental series ranged from 2 03 ± 0 40 to 4 75 ± 0 54 (SE) mV The lowest concentration of CPC (0 21 mM) caused a brief hyperpolarization of 12 to 20 seconds duration followed by an exposure time dependent reduction in PD (Fig 1) As the con centration was increased the maximal reduction in PD as a percentage of the

Table I

Values of hyperpolarization percentage reduction and recovery of corneal potential difference after exposure of the epithelial surface of the *in vitro* rabbit cornea to cetylpyridinium chloride

Concentration and time		Hyper polarization % of original PD	Maximal reduction % of original PD	% recovery after 2 h % of original PD	Time of minimum PD (min)
0 21 mM	1 min	14	58	68	30
	2 min		75	48	60
0 56 mM	1 min	16	90	25	75
	2 min		93	13	45
2 mM	1 min	15	100	0	120
0 56 mM + 2 % pilocarpine + 100 mg % albumin	1 min	340	59	45	30

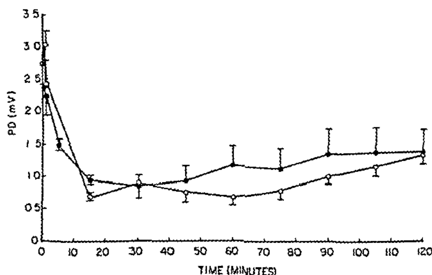


Fig 1

Effect of 0 21 mM cetylpyridinium chloride on the potential difference across the isolated rabbit cornea PD potential difference (mV) ●——● 1 min exposure to CPC ○——○ 2 min exposure to CPC Values are the mean ± SEM

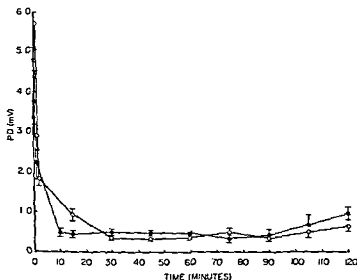


Fig
Effect of 0.56 mM cetylpyridinium chloride on the potential difference across the isolated rabbit cornea For explanation of symbols see legend to Fig 1

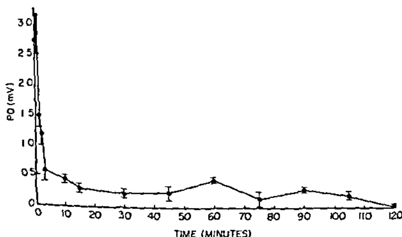


Fig 3
Effect of 2 mM cetylpyridinium chloride on the potential difference across the isolated rabbit cornea The exposure time was 1 min Values are the mean ± SEM

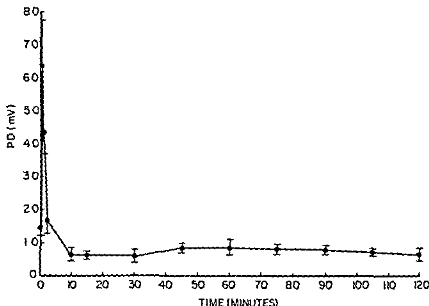


Fig 4

Effect of 0 56 mM cetylpyridinium chloride plus pilocarpine and albumin on the potential difference of the isolated rabbit cornea The exposure time was 1 min Values are the mean ± SEM

original PD also increased (Fig 2) until at 2 mM the PD was abolished at 120 min (Fig 3) The results with 2 % pilocarpine 100 mg % albumin and 0 56 mM CPC in the epithelial bathing solution reveal some differences from the data obtained with Ringer alone in the bathing solution Transfer of the cornea from normal Ringer to Ringer pilocarpine and albumin resulted in a fall of PD of approximately 40 % (2 65 ± 0 40 to 1 45 ± 0 21 mV mean ± SE of 4 corneas) indicating that this solution alone produced a change in epithelial permeability The hyperpolarization phase in the presence of CPC is both greater and of longer duration than with CPC alone (Fig 4) but the maximum depression in PD is similar to that seen with 0 56 mM CPC alone (Table I)

In vivo experiments A similar pattern to the *in vitro* experiments is also seen in the *in vivo* experiments The reduction in PD is concentration dependent since 2 mM causes a greater fall than 0 56 mM (Figs 5 and 6) The exposure time appeared to have no effect on the magnitude of the PD fall except at earlier times With 2 mM CPC for both 1 and 2 min exposure there was still a hyperpolarization at 2 min which was followed by a fall in PD by approximately

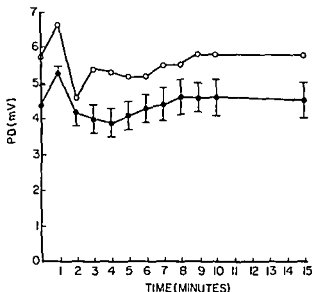


Fig 5
Effect of 0 56 mM cetylpyridinium chloride on the potential difference across the *in vivo* rabbit cornea For explanation of symbols see legend to Fig 1

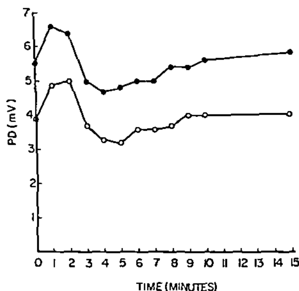


Fig 6
Effect of ? mM cetylpyridinium chloride on the potential difference across the *in vivo* rabbit cornea For explanation of symbols see legend to Fig 1

the same degree With 0.56 mM CPC the initial hyperpolarization only lasted for 1 min even during 2 min exposure and the PD fell less than with 2 mM CPC (Figs 5 and 6)

Anatomy The normal anatomical structure of the epithelium is seen in Fig 7a and b where microvillae and microplicae are abundant on the surface of the epithelial cells With the regimen of one drop x 3 at 0 21 mM there were few changes except possibly more dark cells with these cells having fewer or flatter microplicae At 0 56 mM however there is loss of microplicae from almost all cells (Fig 8a) whereas at 2 mM there is also exposure of underlying cells (Fig 8b) With the regimen of 1 drop x 10 some surface pitting is seen at 0 21 mM (Fig 9a) and at 0 56 mM all cells seem to be altered with apparent holes in the cell membrane (Fig 9b) at 2 mM there is little further change in appearance except that most cells are smooth having lost their microplicae (Fig 10)

Discussion

In many respects the effects of cetylpyridinium chloride (CPC) on the electrophysiology and anatomy of the rabbit cornea parallel those of benzalkonium chloride (BA) which have been reported earlier (Green & Tonjum 1971 1975 Tonjum 1975a b) The electrophysiological responses with an initial hyperpolarization followed by a fall in potential difference (PD) are very similar to those found with BA The recovery of PD also appears to be concentration and exposure time dependent (Table I) The initial hyperpolarization appears to be faster than that seen with BA and this may be a reflection of the much smaller molecular size of CPC since the smaller compound would be able to penetrate the corneal epithelium more readily than the much larger BA molecule Comparing BA (Green & Tonjum 1971 1975 Tonjum 1975a) to CPC indicates that CPC is far more active at least at the concentrations tested

As with BA the *in vivo* effects of the surfactant are less than those seen with the *in vitro* preparation but the changes are qualitatively similar The reduction in PD is much less *in vivo* and recovery is complete within 15 to 30 min compared to the more profound *in vitro* effects Presumably the more rapid recovery

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Fig 7 a and b
Scanning electron micrograph of normal corneal epithelium Note the presence of dark cells All cells have an abundance of microvilli and microplicae
a) x 5000 b) x 10 000

a

b

of the PD and the less marked reduction in PD *in vivo* compared to the *in vitro* cornea reflects a difference in the metabolic status of the *in vivo* and *in vitro* cornea and the ability of the *in vivo* cornea to reestablish the barrier function of the epithelium

The electrical responses of the tissue to CPC in pilocarpine albumin solution is of interest since the hyperpolarization phase is not only substantially greater but is also of longer duration One explanation for this effect is related to the placement of the hypertonic solution on the anterior surface of the corneal epithelium Such a procedure in other tissues such as frog skin (Ussing & Windhager 1964) and toad bladder (Urakabe Handler & Orloff 1970 Wade Revel & DiScala 1973 DiBona & Civan 1973) has been shown to increase the permeability of these membranes to a variety of solutes The decrease in PD when the cornea is moved from Ringer alone to the pilocarpine albumin solution indicates that the permeability of the epithelium is also increased by the hypertonic solution on the outer surface

Schoffeniels Gilles & Dandrifosse (1962) and Webb (1965) observed an initial hyperpolarization of the isolated frog skin with surfactants The hyperpolarization was thought to be the result of a disruption of cellular integrity caused by interactions of the surfactant with membrane located calcium The membrane permeability is thereby increased giving rise to a transient potassium efflux which causes the hyperpolarization The hyperpolarization seen with CPC is presumably related to this increased potassium efflux The excessive hyperpolarization when pilocarpine and albumin are on the epithelial surface is probably related to the fact that the intercellular channels of the epithelium are dilated with hypertonic solutions Thus CPC is able to penetrate into the deeper layers of the epithelium causing a greater hyperpolarization as well as a hyperpolarization of more cells Saladino Hawkins & Trump (1971) examined the effects of CPC on toad bladder but did not observe such a hyperpolarization They did however note an increased oxygen uptake at a time following surfactant treatment equivalent to the electrical changes seen here. The toad bladder recovered from low doses (10) of CPC whereas high doses (10^{-3} M) caused

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Fig 5 a and b

Scanning electron micrograph of corneal epithelium after CPC treatment

a) 1 drop of 0 5(mM CPC 3 times at 30 second intervals Note loss of microplicae from cells An apparently normal cell remains × 5000

b) 1 drop of ? m ι CPC 3 times at 30 second intervals There is loss of superficial cells over much of the epithelium causing exposure of underlying cells × 1000

a

b

apparently irreversible damage (Saladino Hawkins & Trump 1971) Similarly with the cornea the PD recovered from 0 21 mM ($2 1 \times 10^{-4}$ M) but not from a 1 min exposure to 2 mM (2×10^{-3} M)

The data of Mikkelson Chrai & Robinson (1973) can therefore be explained on the basis of the enhancement of permeability caused by CPC since all concentrations tested here (which span the concentration used by Mikkelson Chrai & Robinson by at least three fold in each direction) caused an increase in passive epithelial permeability even *in vivo* The anatomical studies particularly were performed with drops of CPC applied to the *in vivo* corneal surface in the normal manner whereas the electrophysiological studies by necessity required techniques which departed from the normal physiological condition Both the electrophysiological and anatomical data indicates that the PD is reduced by a breakdown of the epithelial barrier located in the superficial epithelial cells (Green 1969) which creates a shunt pathway for the movement of solutes and solvent across the membrane The recovery of the PD is related to the recovery of the barrier function presumably at a deeper location in the corneal epithelium Previously we (Green & Tonjum 1971) described a single dose effect of CPC (2 mM) on fluorescein permeability and found a 28 fold increase in permeability to the dye. The present data substantiate this finding and expand the dose range

While it is obviously true that surfactants such as CPC and BAC (Green & Tonjum 1975) affect the electrical characteristics of the cornea and may affect the fixed surface and tissue charges on the tissue it is equally obvious that the major effect of such agents is to enhance the penetration of drugs particularly ionic forms across the relatively impermeable epithelium This effect is even more pronounced when one considers the clinical situation under which a drug is applied topically to the eye namely one drop which is subjected to immediate dilution and loss via the lacrymal system

The effects of CPC have been examined on the electrophysiology and anatomy of the rabbit cornea The primary effect of CPC at the concentrations tested here is to eliminate the physiological and anatomical barrier to fluid movement

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Fig 9 a and b

Scanning electron micrograph of corneal epithelium after CPC treatment

a) 1 drop of 0 21 mM CPC 10 times at 30 second intervals Surface pitting is evident on several cells × 1000

b) 1 drop of 0 56 mM CPC 10 times at 30 second intervals Apparent holes in cell surface are seen membrane appears to be lattice like × 10 000

a

b



Fig 10
Scanning electron micrograph of corneal epithelium after 2 mM CPC treatment Cells are smooth with loss of most microvilli and exposure of underlying cells There is expansion of intercellular spaces × 2000

in the corneal epithelium by destroying the cell membranes and causing lysis of the cells The sanction of the use of CPC in ophthalmic preparations as a protein drug unbinding agent would on the basis of the present data appear to be premature Only long term testing to determine the toxicity of CPC can assure the safety of this surfactant in ophthalmic preparations

Acknowledgments

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DIAGNOSTIC VALUE OF THE WATER DRINKING TEST IN EARLY DETECTION OF SIMPLE GLAUCOMA

BY

KNUD ERIK RASMUSSEN and HANS ALRØ JØRGENSEN

A series of 64 patients (119 eyes) subjected 10 years previously to water provocative tests on a suspicion of simple glaucoma were followed up At that time the intraocular tension exceeded 20 mmHg but there were no optic disc changes and no visual field defects The follow up examination comprised ophthalmoscopy visual acuity gonioscopy intraocular tension and perimetry Setting a rise of 8 mmHg as the lower limit the water provocative test ten years previously had been positive in 31 eyes Nine of these developed glaucomatous visual field defects despite treatment (29 per cent) The test had been negative in 88 eyes Of these 21 (24 per cent) developed glaucomatous visual field defects
The water drinking test was negative in 70 per cent of the eyes which subsequently developed visual field defects and negative in 75 per cent of those in which no defects developed Thus the test was neither of diagnostic nor of prognostic value
All the eyes with a positive test which later developed visual field defects had been treated whereas 57 per cent of the eyes with a negative test which subsequently developed visual field defects had received no treatment This indicated that a negative water drinking test gave a false security It is shown that an alteration of the lower limit of a tension rise does not render the water provocative test any more useful

Key words simple glaucoma – water provocative test – visual field – cupping of the optic disc – intraocular tension – antiglaucomatous treatment

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Simple glaucoma is still one of the main causes of senescent blindness There fore any examination capable of establishing an early diagnosis with reason able certainty or of bearing out a suspicion of this grave disease is of immediate importance

Several provocative tests have been developed in the course of time in an attempt to separate out the cases predisposed to a manifest glaucoma Of these, the water provocative test is still – in Denmark at least – the most commonly employed test Since its introduction into ophthalmology by Schmidt (1928 1979) several workers (e g Bloomfield & Kellerman 1947 Scheie Spencer & Helmick 1956 Nørskov 1967) have found it to be a suitable method for diagnosing an open angle simple glaucoma

It has been claimed that scleral rigidity decreases during the water drinking test so that values measured with Schiotz weight tonometer are too high (Becker & Gay 1959 Edmund 1960 Drance 1960 1963) Others (Stepanik 1958 Galin Aizave & McLean 1961 a b) found the scleral rigidity to be un *altered* Some disagreement prevails concerning *what constitutes a pathological* rise in tension According to most workers a rise of 6 mmHg should raise suspicion while a rise of 8–9 mmHg is considered as definitely pathological (Sugar 1948 Leydhecker 1954 Blaxter 1956 Nørskov 1967)

The water provocative test has recently been criticized and its usefulness both as a diagnostic and as a prognostic aid has been questioned (Nørskov 1970 Roth 1974) We therefore decided to follow up a group of patients who had been subjected to water provocative test ten years or more previously This was done for the purpose of clarifying whether any difference was detectable between the group with a positive test and that with a negative test with regard to the later development of manifest glaucoma

Material and Methods

All the patients we followed up had at least ten years previously been subjected to a water provocative test as part of an examination for simple glaucoma The reason for this and *the further examination for simple glaucoma was usually a raised tension* (above 0 mmHg) measured at routine tonometry The subsequent control and pos sible treatment were undertaken by the referring ophthalmologists after these had been informed of the result of the test Primarily the Department only yielded the technical diagnostic service

The water provocative test was carried out as described by Nørskov (1967) and others The patients arrived fasting in the morning They had been instructed not to eat or drink after midnight The intraocular tension was measured (in most cases by applanation tonometry in rare cases using Schiotz tonometer) The patient then drank one litre of water within 5 min after which the tension was measured at

10–15 min intervals for about 1 h if no rise was noticed or in case of a rise until the tension had returned to normal A rise of 8 mmHg or higher was regarded as a *positive reaction*

Moreover the patients fulfilled the following requirements Born within the 20th century a normal vision (6/9 or better with optimum correction) on first examination normal visual field (Goldmann or campimetry) normal optic disc and open angles controlled by gonioscopy Among our case records we found 90 patients who fulfilled these *requirements Of these 14 had died while 12 could not or would not appear* for a follow up examination

64 patients or 119 eyes remained These 119 eyes were subjected to determination of visual acuity gonioscopy Goldmann s perimetry measurement of tension and ophthalmoscopy The patients were questioned about possible treatment and observance of this during the past ten years

Results

Without considering the cause of any altered vision (a small number had in the meantime been operated on for cataract) we found 110 eyes with a vision of 6/18 or better while five eyes had between 4/60 and 6/36 and four eyes below 3/60 Goldmann s perimetry could be performed on all the patients except one

The gonioscopic impression of the chamber angle was the same on the first and the second examination In 108 eyes the conditions of the optic disc could be related to those of the visual field In 93 3 per cent of these cases a cor

Table I

Distribution of eyes subjected to water provocative test It is seen how the glaucomatous visual field defects are distributed in the groups with positive and negative water provocative tests and how the treatment is distributed in the two main groups and the groups with and without visual field defects

positive 31	+ glaucomatous visual field defects 9	+ treatment 9
	− glaucomatous visual field defects 22	+ treatment 18
		− treatment 4
negative 58	+ glaucomatous visual field defects 21	+ treatment 9
		− treatment 12
	− glaucomatous visual field defects [illegible]	+ treatment 17
		− treatment 20

relation was noticed between cupping of the optic disc and visual field defects In the remaining cases a normal optic disc together with glaucomatous loss of visual field and the reverse were almost equally frequent In 11 eyes no comparison could be drawn between optic disc and visual field owing to blurring of media and/or miosis

Table I shows how many of the examined eyes reacted positively to the water drinking test and how many did not. Further we see the distribution within these two groups between eyes that after ten years or more had developed glaucomatous visual field defects and eyes with a normal visual field Finally we see how many eyes within the individual groups received treatment and how many did not

30 eyes had developed glaucomatous visual field defects within the observation period In seven of these eyes (six patients) the defects were fairly grave (only 10 per cent or less of the central visual field preserved) Of the 30 eyes 9 (30 per cent) had reacted positively to water drinking while 21 (70 per cent) had reacted negatively Of the 31 eyes with a positive reaction to water drinking 9 (29 per cent) had developed visual field defects The same was true of 21 (24 per cent) of the 88 eyes with negative reaction

The nine eyes with an originally positive water drinking test and visual field defect all received antiglaucomatous treatment

Of the 21 negatively reacting eyes which had developed visual field defects 9 (43 per cent) were given antiglaucomatous treatment while 12 (57 per cent) received no treatment In other words 18 (60 per cent) of the 30 eyes were treated and 12 (40 per cent) not

Table II

Distribution between the different groups in relation to an initial tension of ≥ 24 mmHg

water provocative test	visual field	treatment	tension ≥ 24 mmHg	%
positive	+ defects	+ treatment	1	11
positive	– defects	+ treatment	6	33
positive	– defects	– treatment	0	0
negative	+ defects	+ treatment	–	22
negative	+ defects	– treatment	1	8
negative	– defects	treatment	2	12
negative	– defects	– treatment	0	0

Of the 89 eyes without any visual field defects 22 (25 per cent) had reacted positively and 67 (75 per cent) negatively to water drinking 35 (39 per cent) of these 89 eyes received treatment while 54 (61 per cent) did not

We see that 27 (87 per cent) of the eyes with a positive water drinking test and 26 (30 per cent) of those with a negative test received treatment

If we regard a high initial tension as a prognostic criterion the conditions observed were as shown in Table II Note that the initial tensions were the highest in the groups given treatment whereas no correlation was demonstrated between initial tension and development of visual field defects The figures in the individual groups are however too small to permit any conclusions to be made

At the time of the follow up examination 7 per cent of the eyes had tensions ranging from 24 to over 50 mmHg 13 per cent between 20 and 24 mmHg and 80 per cent 20 mmHg or lower

Discussion

Blaxter (1936) and Norskov (1970) noticed negative water provocative tests in 60 and 70 per cent respectively of eyes with manifest glaucoma We likewise found the test to be negative in 70 per cent of the eyes that had developed manifest glaucoma and visual field defect after ten years of observation The test was negative in 75 per cent of the eyes which had not developed manifest glaucoma with associated visual field defect after ten years Among the patients with a positive water drinking test 29 per cent developed visual field defects The same was true of 24 per cent of those with a negative test Thus the water provocative test afforded no aid towards distinguishing between those patients developing visual field defects and those patients in which no defects developed

The question of the rise in tension required for the test to be characterized as positive has previously been discussed (Sugar 1948 Leydhecker 1954 Blaxter 1956 Drance 1963 Norskov 1967) However the conclusion that the water provocative test is unsuitable as a diagnostic and a prognostic aid would be the same even if we had chosen any other value than 8 mmHg If a lower value had been chosen the number of false positive results would have exceeded the present 71 per cent and many patients might be treated perhaps without treatment being necessary This group of treated patients constituted 82 per cent It is impossible to decide however how many of these patients would have developed visual field defects if left untreated If on the other hand a higher limit had been chosen the number of false negative results

amounting to 24 per cent using a rise of 8 mmHg would have become greater This would have been particularly unfortunate in the series under review this group being definitely exposed to failing motivation for treatment No more than 43 per cent of this group with developed visual field defects were treated unlike the group with a positive water drinking test and defects in which all eyes were treated It is difficult to say why 12 out of 21 patients (57 per cent) were left to develop visual field defects without being subjected to treatment Very likely however the proper reason is that the negative water provocative test had provided the referring colleague with a false feeling of security

Another reason for choosing a value higher than 8 mmHg as the lower limit might be the fact that the test was positive and indicated therapy in no more than 30 per cent of the cases in which visual field defects developed while it was regarded as negative and with no indication for therapy in 75 per cent of those in which no defect developed By raising the limit a value could be obtained at which the test gave the same percentage of errors whether visual field defects occurred or not Such would however give no better diagnostic or prognostic aid than the present limit of 8 mmHg The fairly equal percentages of negative and positive water drinking tests recorded in the two groups with and without developed visual field defect respectively more likely go to show that a possible rise after the drinking one litre of water need not necessarily indicate the presence of simple glaucoma

Accordingly as also pointed out by Nørskov (1970) and Roth (1974) we can probably attach little value to the water provocative test as a diagnostic and a prognostic aid in cases of intraocular hypertension – simple glaucoma More particularly we must warn against reliance on a negative test and a consequent failing control of the patient

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OCCURRENCE OF LYMPHOCYTOTOXIC LYMPHOCYTES AND ANTIBODIES AFTER CORNEAL TRANSPLANTATION

BY

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Twentyfive recipients of penetrating corneal grafts were investigated for the presence in the peripheral blood of cytotoxic lymphocytes by the Direct Cell Mediated Lympholysis (Direct CML) test as well as for lymphocytotoxic antibodies

Eight patients presented a positive Direct CML. Six of these patients have shown clinical signs of graft rejection, while two patients had a clinically uncomplicated course

Only one of the 25 patients had lymphocytotoxic antibodies This patient showed a negative Direct CML and a clinically uncomplicated course

The findings seem to imply that recipients of corneal grafts can be immunized by their grafts and that cytotoxic lymphocytes in peripheral blood appear frequently in those patients showing graft rejection

Key words cell mediated lympholysis – cornea – lymphocytotoxic antibodies – transplantation

Opinions still differ as regards the significance of tissue compatibility for the outcome of corneal grafting ABO compatibility appearently plays only a minor role (Meyer 1971 Allansmith et al 1975) while HLA compatibility seems to

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be of some importance (Ehlers & Kissmeyer Nielsen 1973 Gibbs et al 1973 1974 Watson & Joysey 1973)

Stark et al (1973) observed the development of lymphocytotoxic antibodies in five of six patients whose grafts failed because of allograft rejection and in only one of eight patients following successful treatment of graft rejection Detectable lymphocytotoxic antibodies did not develop in 15 patients who showed no evidence of immune graft rejection

However Jones (1973) stated summing up the present knowledge and problems of corneal graft failure that cell mediated reactions seem to play a major role in corneal graft rejection while the contribution of humoral responses remain uncertain There were no data on Cell Mediated Lympholysis (CML) in Jones (1973) article

The purpose of this study was to investigate a series of corneal graft recipients for the occurrence of cellular and humoral sensitization

Materials and Methods

Twentyfive patients had received one or several 7 mm penetrating corneal grafts No attempts have been made to either match of mismatch the donor/recipient pairs recipient selection has thus been random The applied surgical technique and postoperative care has been published previously (Ehlers & Kissmeyer Nielsen 1973) At varying times after the operation samples of blood were withdrawn and analyzed for cellular cytotoxicity by use of the Direct Cell Mediated Lympholysis (Direct CML) technique From the defibrinated blood lymphocytes were isolated and kept frozen in liquid nitrogen until the day of investigation The Direct CML technique has been described in detail earlier (Grunnet et al 1974 1975) Briefly the lymphocytes from the patients were mixed with Cr^{51} labelled PHA lymphoblasts from four selected normal individuals (targets) These cells possessed 14 different HLA A and B antigens (HLA A1 2 3 9 11 w19 B5 7 8 12 13 w15 w35 w40)

The test tubes were incubated for 6 h under culture conditions and then the radioactivity released from the target cells was counted in a sample of the supernatant In addition the remainder (supernatant and the cell pellet) was counted and the Cr^{51} release percentage calculated as *individual tube release* by the formula

$$\frac{\text{experimental CPM in supernatant}}{\text{total CPM in test tube}} \times 100 - \frac{\text{spontaneous CPM in supernatant}}{\text{total CPM in test tube}} \times 100$$

= release % A release % > 10 % was considered positive (Kristensen & Grunnet 1975)

All the calculations of chromium release % were based on mean CPM (counts per minute) of duplicates

Furthermore serum was taken from the patients and analyzed for lympho cytotoxic antibodies by use of trypanblue exclusion test as described by Kiss meyer Nielsen & Kjerbye (1967)

Results

The pertinent patient data and the experimental results appear from Table I It is seen that eight patients are positive in Direct CML Six of these (patients Nos 18–23) presented clinical signs of rejection of the corneal graft This provides a significant association between graft rejection and positive Direct CML (Fisher P = 0 0003) Patient No 17 has until now had an uncomplicated clinical course (6 months) but has been pregnant five times which may explain the positive Direct CML The other Direct CML positive patient (No 16) showing no clinical signs of response against the graft, had been transplanted three weeks before the present investigation This patients might well present rejection later in the course and will be followed in this respect

Comparison of a complicated clinical course (see Table I patients Nos 18–25) with positive Direct CML reveals a significant association (Fisher P = 0 007)

Only one patient (No 14) had lymphocytotoxic antibodies and in spite of this showed a totally uncomplicated course This patient has been pregnant twice and was cornea transplanted once before the actual transplantation

The correlation between the number of HLA A and B incompatibilities and the CML test is given in Table II Obviously there seems to be no striking influence of the number of HLA A and B incompatibilities for the distribution of patients reacting positive or negative in Direct CML Further only two out of the observed eight positive scorings in Direct CMI could be explained by the HLA A and B antigens mismatched in the transplantation and present on the target lymphoblasts However the number of patients is limited and the target cells do not possess all the known HLA A and B antigens

Discussion

The present study seems to imply that the immune system of a recipient may be stimulated to produce or recall cytotoxic lymphocytes also when the graft is a cornea This observation is an argument for the immunological recognition of

Table I

Data for 25 recipients of penetrating 7.0 mm corneal grafts

Case No	Age years	Sex	Corneal disease	Vascularization	Clinical course U = uncomplicated R = rejection episode(s)	Blood transfusion	Pregnancy	Transpl before actual	Lymphocytotoxic antibodies	Direct CMI
1	33	F	Groenouw I	–	U	–	× 4	–	–	
2	42	F	Groenouw II	–	U	–	× 5	–	–	–
3	50	F	Marginal dystrophy	+	U	× 4	× 2	–	–	–
4	62	M	Endoth. dystrophy	–	U	–	–	× 1	–	–
5	66	F	Endoth. dystrophy	–	U	× 3	× 4	× 1	–	–
6	27	M	Keratoconus	–	U	–	–	× 1	–	–
7	49	F	Keratoconus	–	U	–	–	–	–	–
8	47	F	Herpetic keratitis	+	U	–	× 3	–	–	–
9	61	M	Herpetic keratitis	+	U	–	–	–	–	–
10	[illegible]	F	Herpetic keratitis	–	U	× 1	× 3	–	–	–
11	9	F	Non herp. keratitis	+	U	× 1	–	–	–	–
12	[illegible]	F	Non herp. keratitis	+	U	–	–	–	–	–

13	77	Γ	Non herp keratitis	+	U	–	×2	–	–	–
14	62	F	Non herp keratitis	–	U	–	×2	×1	+	–
15	7?	M	Corrosion	+	U	–	–	–	–	–
16	20	M	Keratoconus	–	U	–	–	–	–	+ (< 1)
17	57	F	Keratoconus	–	U	–	×5	–	–	+ (5)
18	35	F	Herpetic keratitis	+	P (8 13)	–	×2	–	–	– (11) + (13)
19	54	M	Keratoconus	+	R (5)	–	–	×6	–	+ (7)
20	47	I	Herpetic keratitis	+	R (16)	–	×5	–	–	+ (21)
21	47	M	Herpetic keratitis	+	R (13)	–	–	–	–	+ (11)
22	61	M	Herpetic keratitis	+	P (< 1)	–	–	×3	–	– (3) + (10)
23	72	F	Herpetic keratitis	–	R (6)	–	–	–	–	+ (9)
24	71	M	Endoth dystrophy	–	Late clouding	–	–	–	–	–
5	41	Γ	Non herp keratitis	–	Prim graft failure	–	×2	–	–	–

The patients are those being in control during the months September December 1975 Patients who need control tend to be more complicated cases This is the explanation for the large number of rejected corneas
The sign – indicates a piece of negative information
The figures in brackets indicate number of months between actual transplantation and rejection or blood sampling
M male F = female

Table II

Direct CML and HLA A and B incompatibility in corneal allograft recipients

No of HLA A and B incom patibilities	Positive Direct CML No of patients	Negative Direct CML No of patients	% positive of total
1	0	0	/
2	1	2	33 %
3	5	9	35 %
4	2	4	33 %
Total	8	15	

Two donor/recipient pairs (cases Nos 3 and 12 Table I) were not HLA typed

the allograft although the corneal graft is placed in the organism at a so called immunologically privileged place (Barker & Billingham 1973)

The efferent pathway of the immune reaction resulting in graft rejection exerted by cytotoxic lymphocytes is understandable if the graft is vascularized In this study one patient (No 23) rejected her corneal graft without showing vascularization but the Direct CML test was positive indicating that cytotoxic lymphocytes may be responsible for damage of the graft In this case the access may be via the aqueous humour (Jones 1973) or there may have been undetected vascularization

Because clinical rejections of corneal grafts may occur after one or more years it is necessary to observe the patients for long periods after the trans plantation

After these preliminary findings with the Direct CML test using an un specific panel of lymphoblasts as targets it is our intention to improve the design of the investigation by use of target cells from the specific corneal donor and to test the two recipients of the same donor tissue several times in the posttransplantation period in order to study the predictive value of the Direct CML test for the manifestation of clinical rejection The implications of these investigations would then be a better identification of recipients reacting on the graft and would make it possible to start and/or increase the immunosuppressive therapy and thereby improving the overall results of corneal transplantation

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A PORTABLE HEMIANOPSIA TESTER

BY

H BYNKE and A HEIJL

A pocket size static perimeter provided with four test lights one for each quadrant of the visual field has been constructed and applied to 190 visual fields in 91 patients The main advantage of the instrument is its ability to disclose hemianopic defects in bedridden and certain sick patients unable to co operate with other methods including the confrontation test This was performed in 12 fields in 7 patients

Key words perimetric instrument – perimetry – multiple stimulus perimetry – bedside examination – visual field – hemianopsia – quadrantanopsia

Pre requisites for a successfull examination of the visual field are that the subject understands the procedure and is able to keep his eye fixed and his attention concentrated for the duration of the examination In conventional perimetry he must also be seated

Patients who are mentally disturbed as a result of intracranial diseas and young children may lack one or more of these requirements In such cases the confrontation test may be the only feasible method of visual field examination Then the static stimulation with two hands placed symmetrically in the field is much superior to the kinetic confrontation test with one hand

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The former test may disclose even relative hemianopsias but is too crude and simple to permit such variations of the procedure that may be necessary to confirm the existence of a field defect The hands may be replaced by other stimuli e g red targets in order to test the colour saturation This facilitates the detection of relative hemianopsias but also demands more cooperation from the subjects

Many instruments have been constructed especially for bedridden patients but there are also other instruments suitable for bedside examination (Schweigger 1889 Holth 1914 Harrington & Flocks 1954 Krimsky 1965 Ben Tovim 1965 1967 1972 Cohen 1971 1974 Rubey 1972) However none of them has been constructed specifically to suit less cooperative patients and the authors have not published any results relating to such cases

One advantage of certain static multiple stimulus instruments e g Friedmann s Visual Field Analyser (Friedmann 1966) is the short exposure time of the test lights The subject s attention is occupied only momentarily and the exposure time is too short to permit any change of fixation Thus Friedmann s Analyser has been found more suited than the kinetic methods for examination of young children (Bynke & Nordenfelt 1974) However it can not be used for bedside examinations

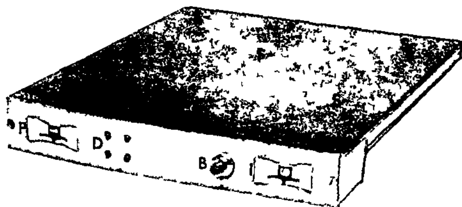


Fig 1
The instrument
S Stimuli F Fixation point P *Step wheel for regulation of position and number* of stimuli D Display B Button for exposure of stimuli I Step wheel for regulation of intensity of stimuli

Modern electronics makes it possible to solve certain problems arising in the construction of small light weight instruments suitable for bedside examinations The purpose of this paper is to describe an instrument combining the advantages of the simple confrontation test and the multiple stimulus instrument mentioned and to demonstrate its suitability for bedridden and less cooperative patients

The Instrument and Its Use

The *instrument is a portable hemianopsia tester* (PHT) *measuring* 15 x 21 x 2.5 cm and weighing 350 g (Fig 1) A central red fixation light and four yellow test lights one for each quadrant of the field have been mounted on a black plate Experience of light emitting diodes (LEDs) as light sources in perimetry (Heijl & Krakau 1975a b) led us to choose them as light sources both for the fixation light and the test stimuli LEDs are stable, respond to square wave currents with square wave light and give a light intensity directly proportional to the current flowing through them When placed 30 cm from the eye being examined the eccentricity of the test lights is 15 degrees One or two test lights or all four may be exposed simultaneously The number and the position of the exposed stimuli are regulated by rotating a 10 step wheel and are indicated by a LED display The intensity of the test lights is chosen by means of another 10 step wheel The ratio between adjacent intensity levels is $\sqrt{2}$ The test lights are exposed for 0 2 seconds by pressing a button. This exposure time has been chosen because it approximately equals the latency time of ocular movements (Westheimer 1954) It is too short to allow *the patient to direct his eye at the stimulus The wheels the display and the* button are situated in a small panel at right angles to the plate with the lights

The instrument is held by the examiner with the plate perpendicular to the visual axis of the eye examined A moderate tilting of the instrument does not noticeably reduce the visibility of the lights which are situated on the plane of the plate By exposing high intensity levels the instrument may be used for bedside examinations in fairly well illuminated wards It is convenient to start the examination by exposing all four test lights at maximal intensity This is then reduced stepwise until fewer than four lights are recognized and so on until no light is seen In deep visual field defects the number of intensity steps between the maximal and minimal number of test lights recognized is large In shallow defects and normal fields this number is small When an appropriate intensity level has been arrived at the examina

tion proceeds at this intensity by changing the number and positions of the test lights In most cases it is enough to use 2 light combinations However in cases of dysphasia dyscalculia or lethargy the procedure may be further simplified by using the four 1 light positions at various intensity levels and asking the patient to point at the lights recognized In any event the whole procedure takes only a few minutes

Material

The material consisted of 190 visual fields in 97 patients 48 males and 49 females aged between 5 and 81 years

The majority of the patients suffered from intracranial diseases such as tumours cerebrovascular lesions and degenerations In some cases intra cranial disease was suspected but could not be confirmed At the time of the present investigation between February and October 1975 or previously they were being treated as in patients in the neurological neurosurgical or other departments of the University Hospital in Lund

The material has been divided into four groups

Group 1 a

50 fields in 27 patients were normal according to kinetic Goldmann perimetry and tangent screen examination

Group 1 b

In 54 fields in 31 patients there were relative hemianopsias or quadrant anopsias These were homonymous in 12 cases bitemporal in 11 and uni ocular in 8 They were confirmed by Goldmann perimetry and/or tangent screen examination The size of these defects varied considerably The majority were of moderate size but some of the bitemporal hemianopsias were small i e only demonstrable within 15 degrees of the fixation point

Group 1 c

In 33 fields in 19 patients there was either a total or subtotal hemianopsia or a quadrantanopsia These defects were homonymous in 13 cases bitemporal in one and uniocular in 5 They were confirmed by Goldmann perimetry tangent screen examination confrontation test or by two of these methods

Group 2

I 27 patients there was a more or less pronounced instability of fixation and a decreased understanding of the procedure because of lethargy senile dementia or young age Seven patients were bedridden and six were children aged between 5 and 9 years

These 27 patients did not cooperate with Goldmann perimetry or tangent screen examination and 14 of them could not even co operate with the confrontation test Among the 13 patients who cooperated more or less satisfactorily in this test, a homonymous hemianopsia was disclosed in one single case In 12 cases the confrontation test was interpreted as negative

These patients like the majority of the other cases in this study were thoroughly examined by neuro radiological and other methods In the tumour cases the diagnoses were verified at the neurosurgical intervention

Methods

Control methods of examination were the quantitative kinetic Goldmann perimetry and the tangent screen examination

With perimetry at least two and in the majority of the cases with defective fields at least three white objects were used Special attention was devoted to exploring the central field

With tangent screen examination white targets of 10 2 and 1 mm were used at a distance of 2 m In 13 less cooperative patients the only control method available was the confrontation test This was performed with single as well as double simultaneous hands In some cases two simultaneous red targets were also utilized

The PHT was used in the manner already described This examination was made on the same occasion as the control methods In 33 patients the examination was started with the PHT and in 50 with the control methods In 14 patients the PHT was the only available method

The Goldmann perimetry was carried out by the authors or by trained assistants whose results were in several cases checked by the authors The other examinations were performed by the authors

Results

The results have been summarized in Tables I II and III They do not appear to be influenced by whether the examination started with the control methods or with the PHT

Table I

The findings of the portable hemianopsia tester in 137 visual fields in 70 patients who were able to co operate with Goldmann perimetry and tangent screen examination

Results of Goldmann perimetry and tangent screen examination	Portable hemianopsia tester (*Nos of fields*)		
	Positive	Questionably positive	Negative
Group 1 a Normal visual fields 50 fields in 27 patients	0	3	47
Group 1 b Relative hemianopsias and quadrantanopsias 54 fields in 31 patients	39	8	7
Group 1 c Total or subtotal hemianopsias and quadrantanopsias 33 fields in 19 patients	33	0	0

Group 1 a

In 47 out of the 50 normal fields no defect could be demonstrated by the PHT One patient with dementia missed some test lights in both fields and another one with a unilateral nasal cataract occasionally missed test lights in the temporal field of that eye Since the answers were varying and inconsistent these 3 fields have been designated as questionably positive (Table I) With all four test lights exposed the intensity range between the maximal and minimal number of recognized test lights was 1–2 steps in this group

Group 1 b

39 out of the 54 relative hemianopsias or quadrantanopsias were demonstrated by the PHT There was full concordance between the PHT and the control methods as regards the position of the defects in these fields In 8 fields (5 patients) defects were also found by the PHT but since their position could not be established they have been designated as questionably positive In 7 fields (4 patients) the defects were missed by the PHT (Table I) In one patient the defects missed were of moderate size and in the others they were

small i e demonstrable only inside 15–20 degrees from the fixation point. The intensity range between the maximal and minimal number of recognized test lights was 2–7 steps in this group

Group 1 c

In all the 33 fields with either total or subtotal hemianopsia or quadrantanopsia the defects were demonstrated by the PHT and their position corresponded to that found by the control methods (Table I) The intensity range was 6–8 steps in this group

Group 2

Among the 27 patients who were unable to co operate with perimetry and tangent screen examination the PHT disclosed defects in 7 (12 fields) (Tables II and III) These defects were homonymous in 5 cases and uniocular in 2 Five of the 7 patients did not even cooperate with the confrontation test In

Table II

The findings of the portable hemianopsia tester in 53 visual fields in 27 patients unable to co operate with Goldmann perimetry and tangent screen examination

Results of confrontation test (Group 2)	Portable hemianopsia tester (Nos of fields)		
	Positive	Questionably positive	Negative
Positive (homonymous hemianopsia) 2 fields in 1 patient	2	0	0
Negative 24 fields in 12 patients	2	2*	0
Not possible 27 fields in 14 patients	8	2	1

* On the basis of clinical symptoms and signs and neuro radiological findings there was no reason to assume any visual field defect in these cases

** Three of these 10 patients had hemi symptoms and positive neuro rad logical findings which might indicate the existence of a homonymous hemianopsia

Table III

Seven patients in whom the portable hemianopsia tester (PHT) revealed visual field defects not demonstrable by other methods

Initials Sex Age (years)	Diagnosis	Clinical signs	Confrontation test	PHT
AS f 9	Laceration rt parieto occipital lobe	Lethargy Lt hemiparesis Asymmetric OKN Choked discs	Not possible	Lt homonymous hemianopsia
KP m 71	Cerebrovascular lesion Diab mellitus	Acquired dementia Epilepsy Lt hemiparesis Asymmetric OKN Diab retinopathy	Not possible	Lt homonymous hemianopsia
BJ m 74	Cerebr atrophy	Gerstmann s syndr Apraxia Memory disturb Reduced CBF esp lt cerebral hemi sphere	Negative	Rt. homonymous inferior quadrantanopsia
HN m 49	Malign glioma rt temporal lobe	Lethargy	Not possible	Lt homonymous hemianopsia
HL m 66	Malignant pituit adenoma	Frontal lobe syndr Lt eye blind Bilateral optic atrophy	Not possible	Temporal hemianopsia rt field
VJ f 16	Cerebral con tusion	Confusion Lt hemiparesis Rt hemiataxia	Lt homo nymous hemianopsia	Lt homonymous hemianopsia and rt homonymous superior quadrantanopsia
NT m 73	Cerebrovascular lesion Arterial hyper tension Rt optic in farction	Lethargy Rt hemiparesis Dysphasia Rt optic disc pale lower half	Not possible	Superior alti tudinal defects rt field Normal lt field

one patient (BJ) this test was interpreted as negative and in another one (VJ) it revealed a left total homonymous hemianopsia.

In the cases of homonymous hemianopsia the lesions in the opposite cerebral hemispheres were demonstrated by neuro radiology and/or were known to exist because of other focal signs In VJ in whom there were severe traumatic cerebral lesions the PHT added the information that there were also homonymous defects in the right superior quadrants The uniocular defects were due to a malignant pituitary adenoma in a patient (HL) whose other eye was blind and an optic nerve infarction in a patient (NT) whose other field was normal Thus in all the positive cases the visual field defects were obviously consistent with other clinical findings (Table III)

Two patients (AS and HL) were examined by both of us independently and with identical results One patient(HN) was reexamined later on when he cooperated with perimetry His hemianopsia was verified on this occasion

In 2 patients (4 fields) questionably positive defects were found by the PHT The other 19 cases (37 fields) were negative according to this method None of them did not cooperate with the confrontation test On the basis of clinical symptoms and signs and neuro radiological findings there was no reason to assume any visual field defects in the questionable positives and in the majority of negatives (Table II)

Discussion

The PHT disclosed 81 or if the questionable positives were excluded 73 out of the 88 hemianopic defects which were demonstrated by the control methods In other words the false negative fields amounted to 8 % and 17 % respectively

Most of the false negative defects were small Some of them were demonstrable only within 15 degrees of the fixation point At a working distance of 30 cm these defects could not be expected to be found by the PHT Another problem in shallow defects was to find the appropriate low intensity level for the examination This was because the intensity steps between the maximal and minimal number of lights recognized with all four test lights being exposed was about equal in shallow defects and in normal fields This problem which is difficult to solve also contributed to the false positive findings and exists in all static multiple stimulus methods (Greve 1973)

It would evidently have been possible to reduce the number of false

negatives by increasing the number of test lights and by testing each field at various working distances We have intentionally refrained from doing this since the primary purpose was to produce a handy instrument able to disclose large and moderate sized defects in less cooperative and bedridden patients The fact that the PHT revealed defects in 5 patients unable to cooperate with the confrontation test and in 2 patients whose defects could not be demonstrated by this test proves that the primary purpose has been achieved

It is easy to overrate a new instrument for visual field examination, if the full capacity of the control methods is not utilized We are aware of this error and have discussed it elsewhere (Bynke & Nordenfelt 1974) However after having used the PHT in clinical practice we are convinced of its value in testing less cooperative and bedridden patients At least it permits an exploration of the paracentral visual field which cannot be performed by the simple confrontation test

Finally it should be mentioned that the PHT may be a valuable supplement to the confrontation test in the hands of non ophthalmologists

Acknowledgment

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THE EPIPAPILLARY MEMBRANE AND THE GLAUCOMATOUS OPTIC DISC

BY

TORD JERNDAL

The frequent presence of an epipapillary membrane as a glial covering of the optic disc is a common source of error when evaluating the cupping of the optic disc in glaucoma
Four instructive cases are documented with colour photographs and field charts

Key words optic disc – cup/disc ratio – glaucoma – glaucomatous cupping – glaucomatous field defect – congenital anomalies – Bergmeister membrane – epipapillary membrane

In 1877 Bergmeister described a glial membrane at the optic nerve head of the rabbit embryo (Fig 1) and this structure is of current interest in the evaluation of glaucomatous cupping of the optic disc According to Seefelder (1910) the glial covering of the optic disc in adult humans is a rudiment of the fetal glial coating of the disc described by Bergmeister Therefore it is called the Bergmeister membrane in the following text This term is chosen to point out its relationship to the fetal Bergmeister papilla and to strees its congenital nature As the hyaloid vascular system involutes and normally disappears in the 8–9th

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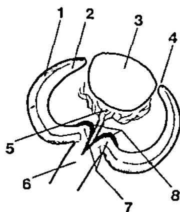
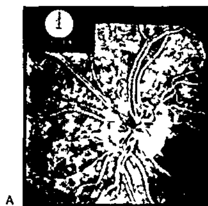


Fig 1

Schematic illustration of a section through the ocular anlage of a rabbit 18 days of fetal age Re drawn after Bergmeister (1877) 1 Outer layer of optic cup 2 Inner layer of optic cup 3 Lens 4 Rim of optic cup 5 Hyaloid vascular cup 6 Optic stalk 7 Fetal optic papilla 8 Cylindric cell layer (future Bergmeister membrane)



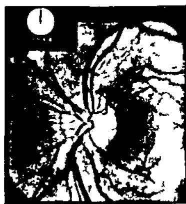


Fig 2

Fig 2A Late fluorescence pattern (36 seconds after injection) of the optic disc and the peripapillary region The bright fluorescence of the temporal part is in strong contrast to the nasal part where a Bergmeister membrane is situated At the peripapillary border between 8 and 12 o clock a crescentic area of fluorescence is apparent outside the membrane

Fig 2B Still later phase of the same sequence (44 seconds after injection) The fluorescence has subsided but the outline of the Bergmeister membrane is still clearly seen as a darker covering of the nasal optic disc (Reproduced with permission from Fluoreszenzangiographie der Retina by Achim Wessing 1968 Georg Thieme Stuttgart West Germany)

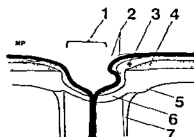


Fig 3

Schematic drawing of central horizontal section through a glaucomatous optic disc The marginal cupping is evident on the left (temporal) side but concealed by the Bergmeister membrane on the right (nasal) side. 1 Apparent cupping of the disc 2 Bergmeister s membrane supported by arterial branch 3 Nerve fiber layer of the retina 4 Choroid 5 Sclera 6 Cribriform plate 7 Dural sheath of optic nerve.

fetal month the glial remnants form epipapillary strand or membranes usually confined to the optic disc and particularly the nasal half (Samuels 1931) This involutional process is not terminated until after birth Therefore the optic nerve head of the newborn displays a dull glial surface of greyish appearance sometimes without a clearcut central cupping In the adult eye discrete glial sheaths are usually seen around the arteries on the disc and rarely also in the immediately peripapillary area A close relationship of the glial sheaths to the retinal arteries is natural in view of the common origin of the hyaloid and the retinal arteries

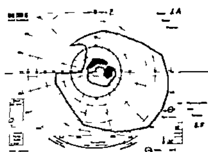
Surface of the Normal Optic Disc

The surface of the adult optic disc is to a variable extent covered by a layer of glia (astrocytes) forming the Bergmeister membrane which at the edge of the disc tapers off into the internal limiting membrane (Samuels 1931) The physiological excavation and the temporal half of the disc is practically free from the Bergmeister membrane

Roth & Foos (1972) in a post mortem material of 504 eyes found on gross examination epipapillary glial membranes in 139 (27 6 %) and thus confirmed the findings of Samuels (1931) The epipapillary membrane was mainly situated on the nasal and nasoinferior aspect of the nerve head and seemed to disappear gradually toward the optic cup Histological verification of the gross observation was obtained in 33 eyes of 34 (Roth & Foss 1972) The membrane consisted of



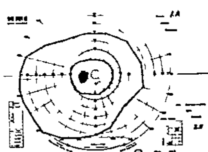
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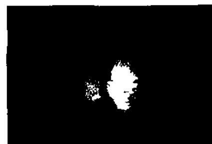
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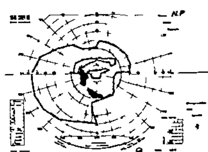
5A



5B



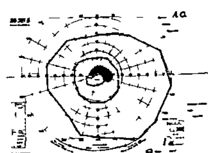
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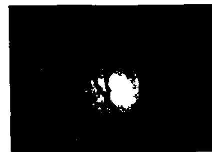
6B



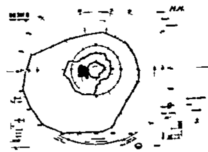
7A



7B



8A



8B

Fig 4 Case 1 I A. Female age 54 Exfol ation glaucoma O D was diagnosed at 53 On f rst e am- inat on *IOP was 56 mm by applanation and a grave defect was found in the superior nasal v sual* field A succesful trabeculectomy normalized the IOP The optic d sc O D is seen in Fig 4A. The excavat on is more pronounced inferiorly and the arteries a e curved along the nasal aspect of the cup A grey glial sheath surround the central stem of the arteries and conceals the nasal under m n ng An annular membrane of greyish orange encircles the per phery of the disc and m ngles w th the arter al sheath Also on the superior aspect of the paracentral disc is a thinner glial membrane best seen with b omicroscopy suspended between the fine arteries runn ng across the disc and its super or edge

Comme t The glial structure described mask the true extent of the excavation but a sli lamp m croscopy revealed the patholog c a atomy Visual f eld shown in Fig 4B

Fig 5 Case 1 I A The nonglaucomatous d sc of O S is seen in Fig 5A and the corresponding field in Fig 5B The t ny excavation is central and demarcated by an ann lar Bergme ster membrane of orange colour A f ne arter al b anch is actually outlin ng the super or rim of the excavat on. (B omicroscop c observat on)

Comment The appearance of the r ght optic d sc (Fig 4A) would hardly have been associated with grave f eld defect had not the extension of the treacherous Be gmeister membrane been ident f ed

Fig 6 Case 2, N P Male age 59 Chron c na row angle glaucoma was d agnosed at 54 w th moderately impa red visual function of O S Because of recurr ng peaks of IOP a trabeculectomy was performed on this eye The optic d sc of O S is seen in *Fig* 6A. The disc is pale and has a d stinctly marginal excavation on the temporal aspect The true w dth of the excavation is very diff cult to assess because of an impress ve glial membrane wh ch covers the nasal third of the d sc and ends abruptly w th a sharp conca e margin n the arter al b furcat on The Be gme ster membrane is supported by several arter al branches and is thereby suspended at a considerable distance f om the bottom of the excavation (B om croscop c observat on) The membrane in this case is grey sh yellow and thick enough to conceal the entry of the retinal vessels The excavation is an extreme example of the vert cally oval cup descr bed by Kirsch and Anderson (1973) The v sual field s demonstrated in Fig 6B The true cond tion of the opt c nerve head was established on sl t lamp m croscopy a 360 marg nal cupp ng w th a probable nasal underm n ng

Comme t The presence of a thick Be gme ster membrane coveri g the nasal th rd of the optic disc obscured the se erity of the glaucomatous cupping

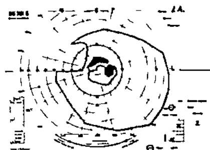
Fig 7 Case 3 A. O Male age 60 B lateral late congen tal glaucoma was d agnosed at 57 O S was bl nd since ch ldhood due to mult ple malformation m crocornea go iodysge esis and coloboma of the iris w th compl cated cataract glaucoma and ret nal detachment O D displayed typ cal gon odysgenes s and a minute choroidal coloboma IOP between 18 and 22 mm by applanat on on m otics and ep nephr ne Very slow prog ess of a superior Bjerrum scotoma. The opt c disc of O D s seen in F g 7A. The ent re disc is co e ed by a cont n ous glial memb ane as seen with the m c oscope No e ca ation can be ident f ed but a deeper ora ge colo r of the disc nasal to the vessels s observed The nasal pos tion of the ascular tree suggests the possibil ty of a glaucomato s excavation unde neath the membrane The glial covering of the margin in the 7 o clock po t on is th n enough to let back lumps of cho oidal p gment shimmer th ough An inferior pe i pap llary halo is seen as well as the m nute cho o dal coloboma at 6 o clock. The v sual f eld is demonstrated in F g 6B

Comme t Maldeveloped eye w th complete covering of the d sc by the Bergme ster membrane Imposs ble to eval ate the true excavation of the d sc in sp te of a growing Bje rum scotoma

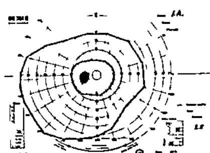
Fig 8 Case 4 M M Female age 61 Dom nant late cong n tal glaucoma O U was d agnosed at 53 and top cal t eatme t was started Because of uncontrolled tension in the fort es trabeculectomy was perfo med b laterally at 59 w th lasting control of tens on The ophthalmoscopic appearance of the opt c d sc O S (Fig 8A) is completely normal with a t ny central excavation and good colour The colou ls of the deep ora ge hue however a d a closer m c oscop c look will e eal an ann la conca e memb aneous cover of the d sc

Comment Once aga n it s helpf l to study the f e arterial branches wh ch suspend the membrane o er the excavat o of the d sc The cha acte s c arc ate scotom fo nd on per metry O S (F g 8B) were at f rst a su pr se in v ew of the normal appea ance of the optic d sc

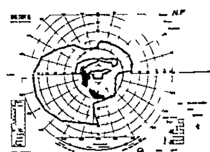

4A


4B

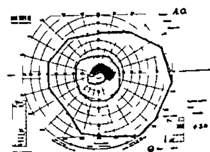

5A

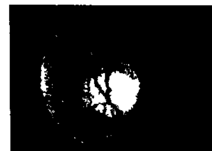

5B

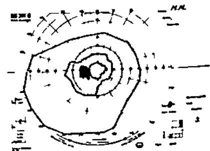

6A


6B


7A


7B


8A


8B

if at all affected by the advancing glaucomatous atrophy of the disc. The most likely reason for the resistance of this membrane to the ischemic degeneration of the optic nerve head is the dual vascularization of this area. The degenerating axons in the prelaminar area are served by the vulnerable choroidal vascular bed which is more easily disturbed by an elevated IOP (Hayreh 1974) The Bergmeister membrane on the other hand is vascularized by the hyaloid retinal circulation

The recognition of the epipapillary membrane on the glaucomatous optic disc is a finding of great practical significance The cup/disc ratio or the volume of the cup becomes a poor measure of the health condition of the optic disc if a study glial lid is masking a rodent excavation underneath This pitfall is clearly demonstrated by the case reports presented The vertically oval shape of the glaucomatous cupping reported by Kirsch & Andersson (1973) is interpreted by me as due to a Bergmeister membrane covering the nasal part of the disc In spite of their astute observations however these authors did not express their recognition of this anatomic structure

The difference in coloration between the nasal and the temporal half of the optic disc on ophthalmoscopic examination has recently been studied by Hayreh (1972) He demonstrated that the relatively pale temporal half of the disc was paradoxically more vascular than the nasal half as judged by fluorescence angiography The pale impression on ophthalmoscopy was explained by a more abundant glial tissue in the temporal part of the disc since according to Hayreh glial tissue is opaque on ophthalmoscopy but transparent on fluorescence angiography The statement by Hayreh that glial tissue (unspecified) is transparent to fluorescent light at first contradicts the observations that the Bergmeister glial membrane may extinguish fluorescence from the corresponding nasal part of the optic disc (Fig 2)

On closer study however these findings are not opposed to one another Hayreh evidently describes only the deeper prelaminar glial structures in the nerve head but not the superficial membrane of Bergmeister

Furthermore he has not made a clear distinction between congenital and proliferative glial tissue In Hayreh s case (1972) showing glial proliferation with *glial veils in front of the retina the histological picture is most likely* one of combined mesenchymal and glial proliferation with a preponderance of the former

Conclusion

An epipapillary glial membrane – the Bergmeister membrane – situated on the nasal aspect of the optic disc is a normal finding on ophthalmoscopy but

is best studied with slit lamp microscopy In advancing glaucoma this membrane may fail to share the degree of atrophy of the underlying axonal tissue as demonstrated by the four presented cases Thus the presence of a Bergmeister membrane will often mask the development of the glaucomatous cupping and may even simulate a normal cup in moderately advanced glaucoma by reflecting a falsely low cup/disc ratio Therefore in the presence of a dubious excavation a slit lamp biomicroscopic examination becomes necessary for a proper evaluation of the glaucomatous cupping

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LENS THICKNESS AND ANGLE CLOSURE GLAUCOMA

A comparative oculometric study in South African Negroes and Danes

BY

VIGGO CLEMMESEN and MAURICE H LUNTZ

A group of Negro patients without ocular disease (normal group) a group of Negroes with angle closure glaucoma and a normal Danish population are compared in terms of anterior chamber depth lens thickness vitreous body length and axial length of the globe It is noted that the normal black population has a significantly thinner lens than the black population with angle closure glaucoma and the normal Danish population The latter two groups have a lens thickness which is similar This finding is discussed in relation to the lower incidence of acute closure attacks in the black population. Attacks of angle closure in this population are generally of the chronic type

Key words lens thickness – angle closure glaucoma – Negroes – Danes – ultrasonography

Read before the 4th Congress of the International Society of Geographical Ophthalmology Edinburgh 1975 Supported by grants from the Danish Medical Research Council and the Witwatersrand University

In 1968 Alper & Laubach (1968) drew attention to the experience that most cases of primary angle closure glaucoma (a c g) seen in American Negroes have a subacute or chronic course while genuine acute attacks are relatively rare At the same time the observation was confirmed by Luntz (1968) as far as South African Negroes are concerned The findings have been analyzed later in detail (Luntz 1973) by the same author who found that angle closure attacks are half as frequent in Negroid patients as in Caucasoids

The aim of the present study was to try to find a structural basis for this clinical difference in the behaviour of angle closure glaucoma

Material and Methods

Both Negroid and Caucasoid patients were investigated The African material comprised 145 normal eyes of Bantu speaking negroes in South Africa (82 persons) Furthermore, 31 eyes of 16 patients suffering from primary angle closure glaucoma were examined The glaucoma patients were attending at the St John s Eye Hospital Baragwanath, Johannesburg The normal eyes were found among non glaucomatous patients in the eye department, in another clinical department and at the Donald Fraser Hospital Sibasa, Northern Transvaal A sample of 102 normal Caucasoid eyes (52 persons) were examined at a Danish hospital for comparison The composition of the material is given in Table I

Ultrasonography

All the measurements were performed using the same technique and equipment an Ekoline 12 ultrasonograph (Smith Kline) Being a portable instrument the accuracy of this equipment is probably not quite as high as that of stationary ultrasonographs (e. g it is not possible to measure the depth of the anterior chamber just as accurately as by pachymetry) However the accuracy has turned out to be adequate for the purpose

Table I
Composition of the material

Sex	Male	Female	Total	Eyes
Normal persons				
Negroids	48	34	82	145
Caucasoids	27	25	52	102
Angle closure glaucoma				
Negroids	11	5	16	31

The instrument used has been compared with stationary equipment by Fledelius & Alsbirk (1975) The Ekoline 12 is provided with a 7.5 M Hz transducer and the range of measurement 0–30 mm was used. In order to prevent fusion of the start pulse and the corneal echo the transducer was fitted with a concave acrylic standoff or contact glass and the cup filled with methyl cellulose The patient was placed in the recumbent position and was asked to look straight upwards

The transducer was placed slowly upon the eye until the four simultaneous echoes from the cornea, the anterior and posterior lens surface and the retina indicated perfect centering of the sound beam At this moment the shutter of the polaroid camera was released. Two measurements were carried out for each eye Each measurement was averaged and corrected according to the velocity in the various ocular media For each sample the following calculations were based on the total number of eyes without regard to sex and right or left eye.

Results

The results are shown in Table II and Fig 1 As expected from our present knowledge it is found that angle closure glaucoma black patients like other angle closure glaucoma patients have shallower anterior chambers thicker lenses

Table II
Ultrasonic ocular biometry

		Anterior chamber depth	Lens thickness	Vitreous body	Axial length
Normal Bantus					
145 eyes	mean	3 19	4 16	15 69	23 05
(mean age 51 8)	SEM	0 073	0 017	0 0 0	0 0 0
	regr coeff	−0 009	0 017	NS	NS
a c g Bantus	mean	2.34	4 81	15.51	2[illegible] 65
31 eyes	SEM	0 036	0 046	0 2[illegible]8	0 243
(mean age 61 0)	regr coeff	−0 0[illegible]0	0 023	NS	NS
Normal Danes	mean	3.34	4 72	15 [illegible]4	23 29
102 eyes	SEM	0 032	0 031	0 06[illegible]	0 0[illegible]7
(mean age 61 4)	regr coeff	−0 003	0 005	NS	NS

SEM standard error of the mean
regr coeff regression coefficient.
NS not significant

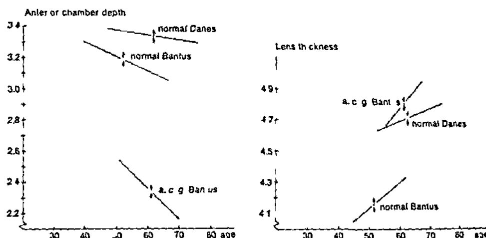


Fig 1

Ocular dimensions anterior chamber depth (cornea included) and lens thickness measured by ultrasonography in Bantu Africans and Danes Arrows show SEM The straight lines are the regression lines showing the age and thickness resp depth range The slopes (the regression coefficients) are given in Table II

and shorter axial lengths than normal black patients However the more noteworthy results is the difference in thickness of the lens between normal Negroids and normal Caucasoids Following an age correction the Bantu lens was still found to be 0 4 mm thinner than that of Danes The ethnic difference is highly significant ($P < 0\ 0005$) ($t \simeq 8\ 5$)

Discussion

The emergence of pupillary block triggering an attack of acute glaucoma is known to depend on a thick anteriorly situated lens It is reasonable to assume that pupillary block will be much less frequent where the lens is thin. It is interesting therefore that in the non glaucomatous black population (the so called normal population) the mean lens thickness was significantly thinner even after correcting for an age difference than in a normal Danish population This difference may explain the lower incidence of acute angle closure attacks in the black population To support our hypothesis that a thinner lens occasions less pupillary block it would be of interest to measure the thickness of lenses in cases of creeping angle closure glaucoma amongst Caucasoid patients The subacute or chronic angle closure attacks seen in Negroes resembles

the creeping angle closure as described by Lowe (1964) and if the lens thickness in Caucasoids with creeping angle closure glaucoma was similar to the lens thickness of the normal black population" this would tend to support the hypo thesis that creeping angle closure glaucoma is assiciated with a thin lens On the other hand it is significant that in black patients who develop angle closure glaucoma the lens was abnormally thick and similar in thickness to a normal Danish population Thus the principle that angle closure glaucoma tends to occur in patients with a thick lens remains true in the black population tested in this investigation

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DEMONSTRATION OF THE HEMIOPIC BORDER IN THE NORMAL PERSON

BY

NIELS EHLERS

The hemiopic border is the vertical line in the visual field separating the two halves which represent each cerebral hemisphere This border which becomes clinically manifest in the hemiopias may be demonstrated in the normal person either (1) by covering an eye with the palm of the hand while facing the sun with the eyes closed or (2) by fixing a near point and observing the background while the two eyes are dissociated by red and green glasses or (3) by two object perimetry in which an inhibition may be observed along the vertical meridian through the fixation point

Key words hemiopic border – two object perimetry – vertical meridian

The visual field of each eye is divided vertically through the fixation area by means of the chiasmal hemidecussation of the optic nerve fibres the line being termed the hemiopic border or the visual vertical meridian Each half field is perceived by the contralateral hemisphere Nevertheless the visual field of an eye is normally perceived as an entity – without even the slightest suggestion of a vertical line of separation and apparently without any differences in perception between the nasal and the temporal fields This state of affairs – however natural it may appear – is in fact quite peculiar

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When an object moves across the hemiopic border the percept must change between the cerebral hemispheres a phenomenon which is not consciously re cognized Torsional movements e g during convergence, will cause the hemiopic border of the two eyes to cross resulting in problems in binocular vision

These examples demonstrate the need for adapting mechanisms along the hemiopic border and it is reported below how it is in fact possible for the normal person to visualize the hemiopic border and to demonstrate an adapting phe nomenon In the literature almost no attention has been paid to this in striking contrast to the overwhelming interest attached to the hemiopias (or hemianopias)

Observations

1 If with the eyes closed one turns to face the sky or any strong light the binocular impression received is that of a bright, red field No sense of form is possible, only lightsense is present When one e e is covered by the palm of the hand the ipsilateral half of the binocular field becomes dark. Naturally it is at once presumed that it is because the corresponding eye is covered But this suggestion is erroneous The temporal hemiretina in the uncovered eye should see the dark half of the binocular field of vision and thus compensate for the occluded eye. The edge between light and dark is vertical and placed in the midline. When the hand is removed after a few minutes the light and dark halves change places an obvious retinal adaptation phenomenon The vertical line is moved with the gaze and remains straight

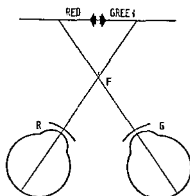


Fig 1

With colour dissociation of the two eyes a separation of the background is seen during convergence The line of separation is sharp vertical and localized to the m dline of the face.

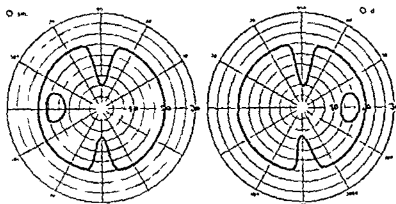


Fig 2
Isopter for two object perception
A wedge shaped zone of inhibition exists along the vertical meridian

2 In binocular vision with a green glass before the right eye and a red before the left a retinal rivalry situation exists Temporal and spatial changes in dominance may occur easily observed when looking at a white screen When an object in front of the *screen is fixated e g a fingertip a vertical separation* of the screen often appears (Fig 1) The right half is green the left is red The line of separation is vertical and localized to the midline The observation may be difficult as it requires a good convergence controlled by the experimentor Many people have been able to verify the phenomenon while others are not convinced It is believed that the *positive* observation in itself proves the existence of the phenomenon

3 By campimetry with two neighbouring horizontally disparate objects the limit of the field of 2 object perception is found as examplified in Fig 2 Within a certain peripheral limit the two objects are perceived as two but along the vertical through the fixation point there are zones in the form of wedges pointing from above and from below towards the fixation point when only one object is seen (Ehlers 19 1 1965)

Comments

With the eyes closed only light perception is possible When for example the right eye is covered the right half of the binocular field of vision is suppressed implicating that basic light perception is mediated through or dominated by the nasal hemiretina supplied with crossed optic fibres

Similarly in the second observation where a near point is fixated the percep

tion of the background is mediated through the nasal hemiretinae the temporal ones being suppressed This dominance of the crossing fibres may be understood phylogenetically The lower vertebrates with lateral eyes have totally crossed optic fibres In mammals with forwardly directed eyes (e g cats and primates) the visual fields of the two eyes overlap and binocular perception of distance becomes possible The overlapping fields are represented by the new un crossed fibres The crossed fibres may be considered as primary or old and therefore dominate certain basic visual functions Thoughts along similar lines have been presented to explain the temporal islands of late glaucoma (Brændstrup 1948) The above arguments are possibly the reason why patients with homonymous hemianopia often consider the eye on the side of the hemiopia as being blind while the contralateral eye is assumed to be unaffected The two situations where the hemiopic border can be visualized must have been seen and overlooked by many Binder & Arndt (1963) reported its occurrence in patients with anomalous retinal correspondence The fact that the observed border is really the hemiopic border should appear obvious from its midline localization and its vertical linear form and the fact that it moves with the gaze What other explanation is possible? It may be added that this visualized border does not show any macular sparing a fact of some interest in the light of the perceptual explanation of macular sparing offered by Verhoeff (1943) The line shows some tilting upon upwards and downwards gaze and upon tilting of the head These aspects and the perceptual displacement of the line to the midline of the head will be discussed in later papers

The 2 object inhibition along the hemiopic border is in principle another way of demonstrating that the field of vision is composed of two half fields When two horizontally separated objects pass the hemiopic border the perception of the first is inhibited

After a certain distance where only one object is seen the first one distinctly reappears and after a further movement the second also becomes distinct This inhibition is a normal phenomenon In a study of seven patients with corpus callosum agenesis it could not be demonstrated (Ehlers 1973) suggesting that it is related to an interhemispheric commisure through the corpus callosum The phenomenon is probably an illustration of an adapting mechanism which links together and normally prevents the realization of the existence of two visual half fields in each eye It may also be of significance in preventing diplopia as a certain overlapping of the two hemiretinae an arrangement known from other sensory nerves probably exists Other functions of this phenomenon may be in the perception of moving objects crossing the border and in binocular visual perception which requires an accurate coordination not only of the two hemiretinae but also of the two eyes and of the two cerebral hemispheres

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BLOOD CIRCULATION CHANGES IN THE EYE AND LIMBS

With relation to pregnancy and female sex hormones

BY

I HØRVEN H GJØNNÆSS and A. KROESE

Alterations in corneal indentation pulse (CIP) amplitudes and pulse volume recordings (PVR) on the limbs were demonstrated in pregnant women indicating that significant changes occur in the peripheral blood circulation during pregnancy

The PVR measured at week 30–36 of gestation demonstrated a significant increase when recorded on the forearm and index finger In the eye an increase in CIP amplitudes was found early in pregnancy From week 20 *on however a steady decrease occurred until the CIP amplitudes at term* averaged about 1/3 of the values from normal non pregnant women Similar changes although less pronounced were demonstrated in the ocular blood circulation during oral contraceptive treatment and to some extent during menstruation Intake of gestagens and diaethyl stilboestrol did not alter the CIP amplitudes

Key words contraceptive treatment – dynamic tonometry – eclampsia – estrogen – gestagen – plethysmography – pre eclampsia – pregnancy – pulse volume recordings

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In previous papers (Hørven & Gjønnæss 1972 1974) a significant reduction of the corneal indentation pulse (CIP) amplitudes was reported to be a characteristic sign of the normal pregnancy This may indicate that the ocular blood circulation is indeed altered during pregnancy In order to collect more information about this phenomenon the present study was performed Groups of patients with complicated pregnancy and patients under medication with various hormones were examined and compared with control subjects

Methods

Dynamic tonometry The dynamic tonometer (Hørven 1968) is an improved standardized electronic Schiøtz tonometer that records eye tension and corneal indentation pulse (CIP) amplitudes at all tension levels The dynamic tonometer output is 1 mV (± 1 %) per micron of plunger movement (Hørven & Gjønnæss 1972) The output is linear The CIP amplitude recorded by dynamic tonometry reflects the pulse synchronous alteration in intraocular pressure which again is dependent on the extra amount of blood (ΔV) that enters the eye in systole The ΔV was calculated in cubic millimeters from the CIP amplitudes by the use of conversion tables based on Langham s and Hetland Eriksen s data (Hørven 1970a) Multiplication with the exact pulse rate gives the ΔV per minute

Intraocular pressure (IOP) was calculated from the dynamic tonometry readings using a 5 5 g plunger weight and Friedenwald s 1955 converting tables (Friedenwald 1957)

Relative crest time determination The crest time is defined as the time in seconds from base to summit of the recorded pulse curve (Dillon & Hertzman 1941)

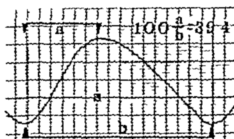


Fig 1
Relative crest time of CIP amplitude is defined as time from base to summit of one pulse curve calculated as a percentage of one pulse cycle

For practical reasons the relative crest time (Horven & Nornes 1971) was calculated as seen in Fig 1.

Pulse rate was calculated from the dynamic tonometry recordings.

Plethysmography Pulse volume recordings (PVR) were performed bilaterally on the forearm proximal and distal index finger the thigh and calf. Before measurements the subjects were supine during 15 min in a room with a temperature between 22–24 C. The arms and the lower limbs were supported by pillows to permit easy cuff application. Recordings of the segmental pulse volumes were performed with a pneumoplethysmograph previously described by Raines (1972) and Darling et al (1972). Appropriate PVR cuffs were placed below the elbow above and below the knee and on the proximal and distal phalanx of the index finger. By means of a hand bulb and atmospheric air a recording cuff pressure of 65 mmHg was obtained. The pulse volume recorder measured and recorded instantaneous pressure changes in the segmental recording cuffs with a chart speed of 5 and 25 mm per second. Cuff pressure changes reflected alteration

Table I

Intraocular pressure pulse rate and dynamic tonometry results in pregnancy

	N	Dynamic tonometry results			
		Intraocular pressure (mmHg) mean (SD)	Pulse rate mean (SD)	CIP amplitudes (μ) mean (SD)	ΔV (mm³/min) mean (SD)
Uncomplicated pregnancy					
week 30–34	12	11.2 (1.9)	87.9 (9.7)	17.7 (4.6)	147.1 (36.8)
week 35–37	12	11.5 (2.1)	95.6 (15.0)	14.6 (4.3)	130.8 (34.0)
week 38–40	30	11.4 (2.0)	90.8 (0.9)	11.8 (5.5)	95.5 (34.5)
Pre eclampsia					
severe	5	13.3 (3.1)	97.3 ([illegible])	11.4 (3)	99.5 (9.5)
moderate	9	12.1 (3.5)	85.1 (10.8)	18.7 (10.3)	148.4 (71.1)
Arterial hypertension	4	13.9 (1.3)	80.9 (14.5)	18.4 ([illegible])	138.6 (85.0)
Non pregnant women	33	14.1 (2.5)	70.5 (9.6)	30.9 (8.6)	207.1 (49.6)

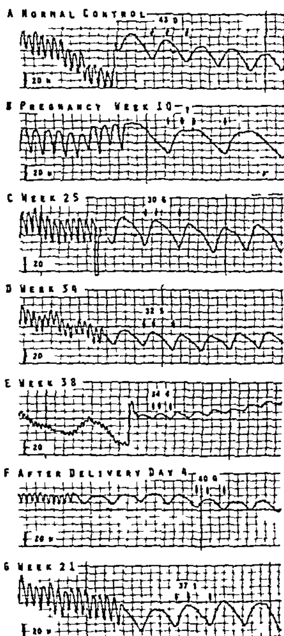


Fig 2

CIP amplitudes recorded before, during and after pregnancy Curves C to G are from same subject Paper speed 5 and 25 mm per second Arrows demonstrate relative crest time evaluations

in cuff volume which in turn reflected momentary changes in limb volume PVR units were calibrated so that 1 mmHg pressure change in the cuff provided a 20 mm chart deflection In the present study pulse volume amplitudes were expressed in mm

Statistics For statistical analysis the Wilcoxon White two sample ranks test or the statistical method of paired comparison were used

Material and Results

Controls

Dynamic tonometry was performed in thirtythree healthy non pregnant women *in the fertile age (18–43 years) The average values of the two eyes are pre* sented in Table I

An average CIP amplitude of 30 9 μ was obtained which is in accord with previous reports for young women (Hørven 1970b) Relative crest time deter minations were performed in 28 of the 33 women an average value of 40.5 % (33 9–46 2) was found

Pregnant women

Normal pregnancy Fifty four women with an average age of 25 / years (15–42) were examined with dynamic tonometry once or more during their normal pregnancies The alteration in CIP amplitudes induced by pregnancy and the decrease in IOP and relative crest time values have been described previously (Hørven & Gjønnæss 1974) The results are summarized in Fig 2 and Table I

During the first half of pregnancy a slight increase in CIP amplitudes was noted together with a slight increase in pulse rate giving a moderate increase in ΔV per min From week 20 on, however a steady decrease was found in CIP amplitudes and ΔV per min (Fig 3) At term the CIP amplitudes averaged about 1/3 of the control value (Fig 2 and Table I)

Plethysmography The pulse volume recordings (PVR) were performed in two groups *of women without signs of cardiovascular disease Ten pregnant women* with a mean age of 25 years (17–33) and a mean brachial blood pressure of 122/73 were examined at week 30–36 of gestation Ten non pregnant women with a mean age of 27 years (21–34) and a mean brach al blood pressure of 125/80 served as controls

The results of the PVR are summarized in Table II and illustrated in Fig 4 Mean pulse amplitudes in the forearm proximal and distal index finger were

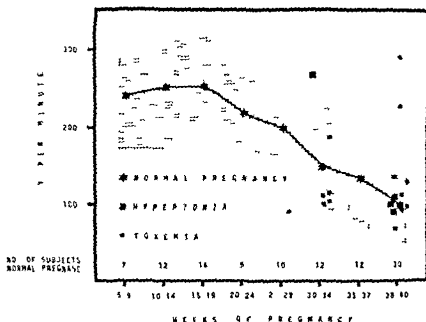


Fig 3

Pulse synchronous change in intraocular volume given as ΔV per min during normal pregnancy The figure offers average values and observed range (stippled area) In addition results obtained in complicated pregnancies (toxemia arterial hypertension) are presented

Table II

Pulse volume recordings

	N	Mean PVR amplitudes in mm				
		Thigh mean (SD)	Calf mean (SD)	Arm mean (SD)	Proximal phalange mean (SD)	Distal phalange mean (SD)
Pregnant women	10	14.8 ([illegible]3)	25 (19.[illegible])	[illegible]5.0 (18.9)	19.[illegible] (6.1)	10 ([illegible]5)
Controls	10	16.3 (5.0)	[illegible]6.0 ([illegible]4)	12.5 ([illegible])	4.9 (3.6)	3 ([illegible]1)
Wilcoxon White				$P < 0.05$	$P < 0.01$	$P < 0.01$

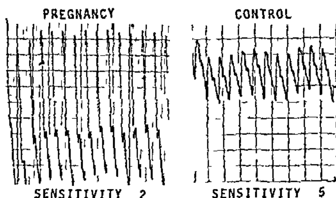


Fig 4

Pulse volume recordings from the proximal phalange of the index finger paper speed 5 mm per second In the pregnant woman the recording was performed with double sensitivity (actual pulse volume amplitude $\frac{46}{2} = 23$ mm) In the non pregnant woman the sensitivity was increased 5 times (actual pulse volume amplitude = $\frac{15}{5} = 3$ mm)

significantly larger in pregnancy (Table II) although no change could be found in relative crest time values The mean pulse amplitudes in the thigh and calf of the two groups were almost identical

Pre eclampsia This groups includes 14 patients with a mean age of 26 6 years 21–38) Five suffered from severe pre eclampsia or eclampsia and had their pregnancies *terminated by Cesarian section in week 29 33 33 34 and 40* re spectively The other 9 patients had moderate pre eclampsia which required no surgical intervention The results are given in Table I and Fig 3

When the ΔV per min of the 5 patients with severe pre eclampsia was com pared with the results of the 12 patients with normal pregnancy examined at a corresponding time of gestation (week 30–34 (Table I)) a difference was found with lower values in the severe pre eclampsia group ($P < 0.02$ Wilcoxon White) However only 5 patients with severe pre eclampsia were examined and one of them first at week 40 of gestation With one exception they showed values within the normal range of uncomplicated pregnancy (Fig 3) Too much importance should not be laid on this difference Thus dynamic tonometry seems to be of no value for the clinical distinction between uncomplicated and pre eclamptic pregnancy

Arterial hypertension Four patients with a mean age of 27 7 years (20–39) de monstrated arterial hypertension during their otherwise uncompl cated preg

nancies (Mean blood pressure Systolic 165 (135–185) Diastolic 116 (100–140) mmHg) These patients showed no significant difference from uncomplicated pregnancy (Table I Fig 3)

Non pregnant women

Effect of normal changes in hormone production during menstrual cycles Six women were examined 4–6 times through one menstrual cycle Although inter individual variations in the ΔV per min values occurred to a large extent, as shown in Fig 5 the intra individual variations were small and did not exceed ± 20 % of the average value Thus the CIP amplitudes and ΔV per min values to some extent seem to be a characteristic for the individual subject. As seen in Fig 5 no change in ΔV per min occurred during the menstrual cycle The relative crest time showed a rather constant decrease one week prior to and during the period (Fig 6) However the changes were not pronounced and not comparable to those seen during pregnancy (Horven & Gjønnæss 1974) although a relative crest time value of 29 7 % was found in one of the subjects during menstruation (Fig 6)

Effects of oral contraceptives Twelve women with a mean age of 2[illegible] 8 years (19–43) were examined by dynamic tonometry without and during oral contra ceptive treatment (Eugynon = Norgestrel (NFN) 0 5 mg ethinylestradiol (NFN) 50 μg) The results are given in Table III Statistically significant decreases were demonstrated in CIP amplitudes and ΔV per min during the medication to 8[illegible] % ($P < 0\ 005$) and 8[illegible] % ($P < 0\ 001$) respectively

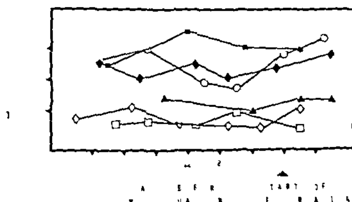


Fig 5
Pulse synchronous change in intraocular volume given as ΔV per min recorded in 6 women at repeated intervals through one menstrual cycle

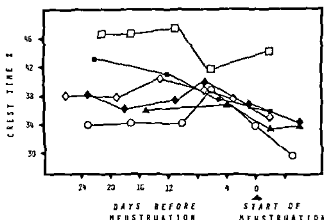


Fig 6
Relative crest time evaluation of the CIP amplitudes recorded at repeated intervals through one menstrual cycle in 6 women

Effect of diaethyl stilboestrol Thirteen girls with an average age of 13 5 years (12–16) were examined by dynamic tonometry during daily intake of either 2 5 mg (3 patients) or 5 mg (10 patients) of the strong non steriodal estrogen compound diaethyl stilboestrol The medication was used in order to inhibit their growth Six girls with no medication and with a mean age of 12 8 years (12–13 5) were used as controls No significant difference was found between the two groups

Table III
Dynamic tonometry results in 12 women without and during daily intake of oral contraceptives

Oral contraceptives	CIP amplitudes (μ) mean	(SD)	ΔV (mm³/min) mean	(SD)
No	31 8	(7 9)	211 8	(48.5)
Yes	27.5	(6 6)	184 7	(41 5)
Statistical method of paired comparison	$P < 0\ 005$		$P < 0\ 001$	

Effect of gestagen. Two women, 50 and 52 years of age, were examined by dynamic tonometry before and during treatment with heavy doses of gestagen given because of malignant disease. They had received a daily dose of 1000 mg oxiprogesteroni caproas im for 5 and 7 days, respectively, when the second examination was performed. The CIP amplitudes and ΔV per min values were unaffected by the medication.

Comment

The main finding in the present study is alterations in CIP amplitudes in pregnancy. In the first trimester an increase was observed, which probably is an effect of the increased stroke volume which has been noted as early as in 8–10 week of pregnancy (Hytten & Leitch 1971). The present finding of significantly larger pulse volume amplitudes in the forearm and index finger of pregnant women compared to non pregnant controls could be explained by the increased stroke volume in addition to a widened pulse pressure and a lower peripheral resistance (Metcalfe & Ueland 1974). The increased PVR in the upper extremity of pregnant women agrees well with reports on other hemodynamic changes during pregnancy. *An increased blood flow in the hand* (Abramson et al. 1943) and forearm (Jansson 1969, Spetz 1964) and increased digital pulsations recorded photographically (Herbert et al. 1958).

Increased peripheral blood flow during pregnancy is probably mainly due to skin flow (Jansson 1969, Spetz 1964). Since skin constitutes a larger portion of the total volume of the finger and forearm than of the thigh and calf, the influence of changes in skin flow during pregnancy may therefore be mainly manifested in the upper limb. This agrees with the findings in the present study of unsignificant differences in PVR of the lower limb and with previous reports on unsignificant differences in calf flow during pregnant and non pregnant states.

After the 20th week all the pregnant women showed progressive decreases of CIP amplitudes and ΔV per min (Fig. 4). These parameters were normalized first 20–30 weeks after delivery (Horven & Gjønnæss 1974). The increased pulse rate during pregnancy can only to a minor extent be held responsible for the CIP amplitude reduction and not at all for the decrease in ΔV per min (Horven & Gjønnæss 1974). A possible explanation for the decrease in ΔV per min is that the extra amount of blood which enters the eye during systole does not induce a corresponding rise in intraocular pressure because of a reduced peripheral resistance and a decreased pressure in the episcleral veins permitting an easier escape of the blood. In the latter part of pregnancy these changes may

overcome the effect of the increased cardiac stroke volume at least in the ocular circulation Reduced pressure of episcleral veins have recently been found during pregnancy (Wilke 1975) this may also explain the decrease observed in IOP during normal pregnancy (Table I)

In the supine position the pregnant uterus will cause a reduced venous blood flow to the heart thereby causing a reduced cardiac output (Hytten & Leitch 1971) which also may be a factor in explaining the small CIP amplitudes in the last trimester of pregnancy However this effect of the supine position disappears abruptly at delivery

Similar changes in CIP amplitudes and ΔV per min as observed during pregnancy was also found to a minor extent during oral contraceptive treatment which also in other respects induces changes similar to those of pregnancy

Acknowledgment

The kind cooperation of Dr Olav Trygstad MD Pediatric Department, Rikshospitalet in sending us patients is gratefully acknowledged

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ÜBER DAS VERHALTEN DES INTRAOKULAREN DRUCKES NACH DER KATARAKTOPERATION IN MIKROCHIRURGISCHER TECHNIK MIT KORNEALEM STUFENSCHNITT UND FORTLAUFENDER NYLONNAHT

VON

L. CORYDON und J DUPERRÉ

Die Druckregulation nach Kataraktoperationen wurde untersucht. Die Operationen wurden mit mikrochirurgischer Technik unter Anwendung eines kornealen Stufenschnittes ab externo und fortlaufender Naht mit Nylonfaden (20 μ) ausgeführt Normale Druckwerte fanden sich sowohl in den ersten Stunden als auch in den ersten Tagen nach dem Eingriff Die Ursache dieser erhaltenen guten Druckregulation liegt wahrscheinlich in einem für den Kammerwinkelbereich sehr schonenden Operationsverfahren

Key words Intraokularer Druck – Kataraktoperation – Kornealer Stufenschnitt – Fortlaufende Nylonnaht

In der Literatur besteht keine Übereinstimmung in der Frage wie sich der intraokulare Druck unmittelbar nach einer Kataraktoperation verhält (Giardini & Paliaga 1964 Gormaz 1962 Harden & North 1972 Hilding 1955 Miller & Morin 1968 Rich 1968 1969 Rich Radtke & Cohan 1974 Witmer & Kreienbühl

Received February 9 1976

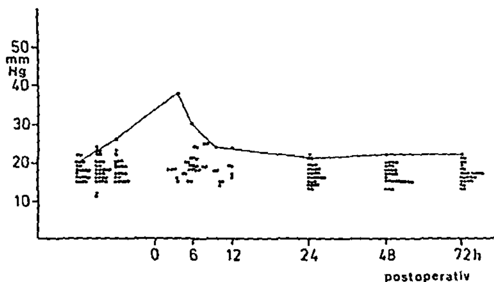


Abb. 1
Am operierten Auge gemessene Druckwerte. Durchgezogene Linie: der einzige Fall mit deutlichem Druckanstieg postoperativ

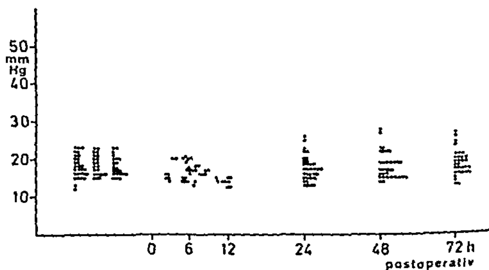


Abb. 2
Am nicht operierten Auge gemessene Druckwerte.

1971) Einige Autoren aber besonders Rich Radtke & Cohan (1974) fanden bei dichtem Wundschluss unmittelbar nach der Kataraktoperation hohe Druckwerte in allen von ihnen untersuchten (24) Fallen Auch Harden & North (1972) registrierten bei gutem Wundschluss postoperativ erhohte Druckwerte

Um die Druckverhaltnisse kurz nach Kataraktoperationen die mit mikro chirurgischer Technik kornealem Stufenschnitt ab externo und fortlaufender Nylonnaht durchgefuhrt worden waren zu untersuchen wurde bei 35 Patienten der Augendruck vor und nach der Operation untersucht (Abb 1 and 2)

Methodik

Der Augendruck wurde mit dem Hardapplanationstonometer (nach Draeger) in der 3 praoperativen Tagen unmittelbar nach dem Eingriff in moglichst dichter Folge (beginnend etwa 3 Stunden nach der Operation) und stets nach 24 48 und 72 Stunden gemessen Sowohl das operierte als auch das nicht operierte Auge wurde untersucht Die Messungen erfolgten stets am liegenden Patienten.

Alle Operationen dieser Studie verliefen ohne Komplikationen auch der postoperative Verlauf aller Falle war normal Die Extraktion erfolgte stets mit dem Kryostab Nur in 5 Fallen wurden postoperativ Mydriatika verabreicht. In 3 Fallen wurden postoperativ lokal Kortikosteroide verwendet Bei 3 Patienten wurde die Extraktion mit Alpha Chymotrypsin ausgefuhrt, da sie junger als 50 Jahre waren In einem Fall trat nach der retrobulbaren Anasthesie ein retrobulbares Hamatom auf

Um einen Eindruck uber das postoperative Druckverhalten verglichen mit den pra operativen Werten zu gewinnen, wurde der Wilcoxon Test durchgefuhrt Als Ausgangswert wurde fur jedes Auge der Mittelwert der (gewohnlich 3) praoperativen Messungen benutzt Die Patienten bei denen mit Alpha Chymotrypsin extrahiert wurde und der Fall mit retrobulbarem Hamatom wurden nicht in diesen Test einbezogen da sie nicht als reprasentativ fur eine normale Kataraktoperation angesehen werden konnen Bei einem weiteren Patienten schwankte der Druck beider Augen praoperativ zwischen 15 und 29 mmHg Auch dieser Fall wurde nicht in dem Test einbezogen

Resultate

Die postoperativen Druckveranderungen waren bemerkenswert gering (Abb 3 and 4) Nur in einem Fall (durchgezogene Linie in Abb 1) stieg der Druck post operativ deutlich an. Hier schwankte jedoch die Tension beider Augen schon vor der Operation zwischen 20 und 26 mmHg

Die Druckwerte der operierten Augen waren 5 und 9 Stunden nach der Operation gegenuber den Ausgangswerten nicht statistisch signifikant verandert wahrend sie 24 48 und 72 Stunden postoperativ statistisch signifikant ($P < 0\ 05$)

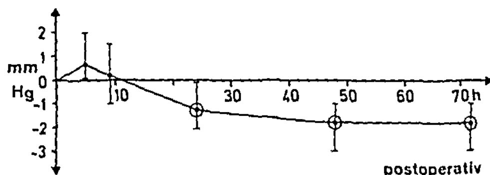


Abb. 3

Durchschnittliche postoperative Druckveranderungen gegenuber dem Ausgangswert (berechnet nach dem Wilcoxon Test) am operierten Auge. Die mit ○ gekennzeichneten Werte unterscheiden sich durch statistische Signifikanz gegenuber dem Ausgangswert

niedriger lagen als vor dem Eingriff. Die Veranderungen waren jedoch gering (bis maximal 2 mmHg). Interessant ist, dass auch die an den nicht operierten Augen 5, 9 und 24 Stunden postoperativ gemessenen Druckwerte statistisch signifikant niedriger lagen. Diese Veranderungen waren ebenfalls gering und die Vermutung liegt nahe, dass dies mit der Pramedikation zusammenhangen konnte. Auch bei den jenigen Patienten, deren Linse mit Alpha Chymotrypsinanwendung extrahiert wurde, blieben die postoperativen Druckwerte normal. Selbst bei dem Patienten mit retrobulbarem Hamatom und bei dem Patienten mit praoperativ stark schwankendem Druck waren die Druckwerte nach der Operation normal.

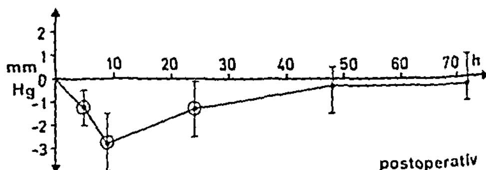


Abb. 4

Durchschnittliche postoperative Druckveranderungen gegenuber dem Ausgangswert (berechnet nach dem Wilcoxon Test) am nicht operierten Auge. Die mit ○ gekennzeichneten Werte unterscheiden sich durch statistische Signifikanz gegenuber dem Ausgangswert

Diskussion

Rich Radtke & Cohan (1974) sowie Harden & North (1972) sahen als wahrscheinliche Ursache einer postoperativen Druckerhohung einen zu dichten Wundschluss an Under den 20 Fallen die Rich Radtke & Cohan (1972) untersuchten waren 9 denen eine intraokulare Linse eingepflanzt war Rich (1969) nahm auch bei kornealen Schnitten eine indirekte Schadigung des Kammerwinkels durch die Operation an Dass die Ursache postoperativer Druckerhohungen moglicherweise in Schadigungen des Abflusssystems zu finden ist deuten auch Arbeiten von Racz Szilvassy & Pinter (1974) sowie von Pur (1969) an Sie fanden dass korneosklerale Schnitte oft die Kammerwinkelstrukturen beruhrten Ausserdem fanden sie ausgepragte Goniosynechien Miller Keskey & Becker (1957) fanden sowohl beim Korneoskleralschnitt als auch beim Kornealschnitt postoperativ erhohten Abflusswiederstand sowie ausgepragte Goniosynechien

Die hier dargestellten Ergebnisse zeigen einen bemerkenswert geringen Einfluss der Kataraktoperation auf die postoperative Druckregulation Dies deutet auf ein schonendes Operationsverfahren mit minimaler Storung im Kammerwinkelbereich hin Dass der Wundschluss bei der hier studierten Operationsmethode (kornealer Schnitt mit fortlaufender Naht) sehr zuverlassig und dicht ist wurde fruher gezeigt (Corydon 1976)

Die postoperative Druckregulation kann demnach nicht etwa auf eine Fistulation aus der Wunde erklart werden

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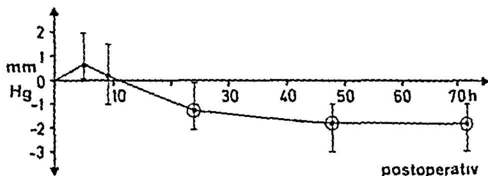


Abb. 3

Durchschnittliche postoperative Druckveränderungen gegenüber dem Ausgangswert (berechnet nach dem Wilcoxon Test) am operierten Auge. Die mit ○ gekennzeichneten Werte unterscheiden sich durch statistische Signifikanz gegenüber dem Ausgangswert.

niedriger lagen als vor dem Eingriff. Die Veränderungen waren jedoch gering (bis maximal 2 mmHg). Interessant ist, dass auch die an den nicht operierten Augen 5, 9 und 24 Stunden postoperativ gemessenen Druckwerte statistisch signifikant niedriger lagen. Diese Veränderungen waren ebenfalls gering und die Vermutung liegt nahe, dass dies mit der Prämedikation zusammenhängen könnte. Auch bei den jenigen Patienten, deren Linse mit Alpha-Chymotrypsinanwendung extrahiert wurde, blieben die postoperativen Druckwerte normal. Selbst bei dem Patienten mit retrobulbärem Hämatom und bei dem Patienten mit präoperativ stark schwankendem Druck waren die Druckwerte nach der Operation normal.

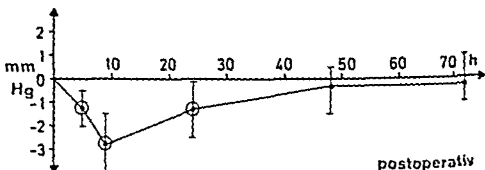


Abb. 4

Durchschnittliche postoperative Druckveränderungen gegenüber dem Ausgangswert (berechnet nach dem Wilcoxon Test) am nicht operierten Auge. Die mit ○ gekennzeichneten Werte unterscheiden sich durch statistische Signifikanz gegenüber dem Ausgangswert.

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CENTRAL CLOUDY CORNEAL DYSTROPHY OF FRANÇOIS

BY

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A family is reported with central cloudy dystrophy of the cornea as described by François in 1956 The lesion consists of a grey zone deep in the stroma, made up of polygonal or rounded areas with indistinct margins separated by apparently clear normal stroma No deposits are visible in the slit lamp The anterior and posterior boundary layers appear normal The corneal thickness is normal Open angle glaucoma was present in the family The pathogenesis of the dystrophy is unknown and histopathological examination has not been described. The differential diagnosis is briefly discussed The family tree is suggestive of a dominant mode of transmission

Key words cornea – dystrophy – glaucoma – heredity – tonometry

In 1956 François described a corneal dystrophy visible only with the slit lamp affecting the deep (posterior) layers of the central stroma The lesion consisted of cloudy grey areas with indefinite structure and indistinct margins The endothelium and epithelium were unaffected François described eight cases ranging in age from 35 to /6 years two were members of a sibship of five while the remaining six cases were sporadic The visual acuity was not affected

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There have only been a few reports on this dystrophy François & Neetens (1957) described a further case in a family with central speckled corneal dystrophy This coincidence was also observed by Collier (1964) who described a 72 year old woman with speckled dystrophy in both eyes and central cloudy dystrophy in one eye Collier (1965) described another case in one of two sisters who both suffered from pseudoxanthoma elasticum The 17 year old son of this patient had some fine opacities in the posterior third of the corneal stroma in one eye Collier (1966) also reported a case in a 77 year old man whose son was found to have a predescemetic dystrophy A family with five affected members was reported by Strachan (1969) The age of the affected members ranged from 8 to 77 years The pedigree showed inheritance of the trait in three successive generations and was suggestive of a dominant mode of transmission

Family J

All 24 members of the family (Fig 1) were examined The examination comprised visual acuity slit lamp examination with measurement of central corneal thickness and corneal diameter ophthalmoscopy applanation tonometry and perimetry a m Goldmann

Report of affected cases

I 2 An 89 year old man who was in good health apart from open angle glaucoma and senile cataract Visual acuity in both eyes 0 4 with correcting glasses Biomicroscopy revealed cloudy grey areas with indistinct margins in the posterior layers of the central

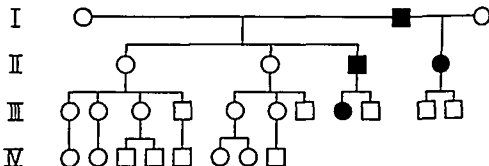


Fig 1

Family tree showing four members affected by central cloudy dystrophy I 1 and I.3 were not examined as they were deceased The proband is II 3

corneal stroma Clear corneal stroma was noted between these areas The epithelium and endothelium were normal Central corneal thickness in both eyes 0.540 mm and corneal diameter 13 mm Gonioscopy revealed normal open angles Repeated applanation tonometry showed a tension of about 32 mmHg in both eyes without medication. Manometric control of the applanation tonometry revealed an additive correction of -1 5 mmHg corresponding to the measured central thickness of the cornea (Ehlers Bramsen & Sperling 1975) Bilateral nuclear cataract was present Ophthalmoscopy showed glaucomatous cupping of both optic discs Perimetry demonstrated bilateral glaucomatous field defects

II 3 The proband a 47 year old man was referred to the Eye Department because of ocular hypertension Visual acuity in both eyes 1 0 emmetropia Biomicroscopy revealed cloudy grey areas with indistinct margins in the posterior layers of the central corneal stroma Normal corneal stroma was observed between these areas (Fig 2) The epithelium and endothelium were normal The anterior chamber was normal the lens was clear Central corneal thickness in both eyes 0 5 0 mm Corneal diameter in both eyes 13 mm Applanation tonometry 19–20 mmHg Gonioscopy ophthalmoscopy and perimetry were normal

II 4 A 43 year old woman Visual acuity in both eyes 1 0 emmetropia Biomicroscopy showed cloudy grey areas with indistinct margins in the posterior layers of the central corneal stroma Normal corneal stroma was noted between these areas The epithelium and endothelium were normal Central corneal thickness in both eyes 0 545 mm Corneal diameter in both eyes 13 mm Applanation tonometry 20–20 mmHg Gonioscopy ophthalmoscopy and perimetry normal

III 8 A 16 year old woman Visual acuity in both eyes 1 0 emmetropia Biomicroscopy revealed cloudy grey areas with indistinct margins in the posterior layers of the central corneal stroma The changes were similar to but not so distinct as in the former cases Normal corneal stroma was seen between the cloudy areas The epithelium and endo

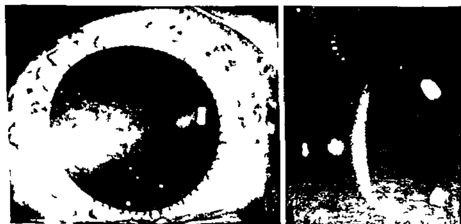


Fig 2

Slit lamp photographs of central cloudy dystrophy Case II

thelium were normal The anterior chamber and lenses were normal Central corneal thickness in both eyes 0 540 mm

Corneal diameter in both eyes 12 mm Applanation tonometry 1⁄–1⁄ mmHg Gonioscopy ophthalmoscopy and perimetry were normal

In summary the slit lamp examination of 4 members of the family showed cloudy grey areas with indefinite structure and indistinct margins affecting the posterior layers of the central stroma and separated by clear apparently normal stroma The epithelial and endothelial boundaries appeared normal and the central corneal thickness was normal The findings are illustrated in Fig 2

Referring to the family tree the disorder appears to be transmitted as a dominant trait This is particularly supported by the fact that patient I 2 has affected children from two different marriages

Discussion

François described central cloudy dystrophy as a lesion consisting of cloudy grey areas with indefinite structure and indistinct margins localized to the posterior or deep half of the corneal stroma with normal boundary layers This description also applies to the cases of the family reported in this paper The observed normal central thickness is another indication of a normally functioning endothelium It may be concluded from the known pedigrees that the lesion is dominantly inherited

The principal corneal dystrophies namely granular dystrophy (Groenouw I) macular dystrophy (Groenouw II) lattice dystrophy and crystalline dystrophy are now well described both from the clinical and from the histopathological and ultrastructural points of view These dystrophies are all located superficially in the stroma whereas the central cloudy dystrophy has a predescemetic position

In most cases it is easy to differentiate central cloudy dystrophy from the other predescemetic dystrophies Cornea farinata is a senile alteration occurring bilaterally and characterized by small rather distinct opacities in the posterior part of the stroma visible only with slit lamp examination under high magnification (Duke Elder 1965 Crayson & Wilbrandt 1967) Dystrophia corneae filiformis profunda (Maeder & Danis) appears as thin white greyish thready distinct areas localized immediately in front of the membrane of Descemet (Eggers & Yaluf 1967 Younessian & Houber 1968) Posterior polymorphous corneal dystrophy of Schlichting is also localized to the immediate predescemetic layers of the cornea and appears as irregular wavy lines extending to the limbus (Boruchoff & Kuwabara 1971 Hanselmayer 1972)

The pathogenesis and histopathology of central cloudy dystrophy remains unknown No biochemical abnormality has been demonstrated A similarity to the corneal changes found in dysproteinaemia has been noted (Gloor 1968) However the serum electrophoresis of patient II 2 was normal

Relation of dystrophy to glaucoma

The four patients with central cloudy dystrophy showed an intraocular tension at the upper limit of normal and the 89 year old patient (I 2) had manifest chronic open angle glaucoma On the assumption that the applanation tensions could be erroneous due to altered mechanical properties of the dystrophic stroma a direct comparison was made in patient I 2 between manometric and applanation pressure The method has previously been described (Ehlers et al 1975) Following retrobulbar lidocaine adrenaline anesthesia a small canula was passed into the anterior chamber The intraocular pressure was determined by the height of a saline reservoir above the eye and simultaneous applanation tonometry was performed with the Draeger hand held applanation tonometer It was found that the applanation value was correct when the previously published correction for corneal thickness was applied This suggests that the central cloudy dystrophy does not affect the mechanical properties of the cornea in such a way that it interferes with the applanation tonometry

In the cases of François (1956) the pressure measured by Schiotz tonometry was 18 to 20 mmHg In the reports of Collier and of Strachan the pressures are not mentioned

Rubenstein & Silverman (1968) described a family with a hereditary deep dystrophy of the cornea and an increased intraocular tension There were no visual field defects and no glaucomatous cupping of the discs The affection differed from central cloudy dystrophy in showing dystrophy of the endothelium and ruptures in Descemet s membrane The chronic glaucoma in our patient I 2 may be a coincident finding but the possibility remains that both diseases are part of some general mesodermal dysplasia and that the other affected members of the family may later develop glaucoma

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VISUAL FUNCTIONS AFTER PERINATAL MACULAR HAEMORRHAGE

BY

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Perinatal macular haemorrhage has been suggested as being a cause of amblyopia and strabismus 39 of 48 *children with macular haemorrhage* after birth were examined at the age of 5 years The study comprised visual acuity with E test types and cycloplegic refraction. Binocular function was evaluated by cover test and 4d prism test Fixation was studied by an ophthalmoscope with a central dark star Sensory function was estimated by Schober test and Worth 4 dot test
The observations gave no support to the existence of organic amblyopia or strabismus following perinatal macular haemorrhage.

Key words macular haemorrhages – haemorrhages in the newborn – amblyopia – strabismus

Retinal haemorrhages are known to occur in a large fraction of newborns The figures range from a few to 50 per cent or even higher

During the years 1969–71 a consecutive series of deliveries was examined by ophthalmoscopy (Ehlers Krarup Jensen & Brogaard Hansen 1974) The series was planned as a comparison of deliveries by means of forceps and vacuum extractor and comprised a total of 413 newborns Ninety nine babies were delivered by forceps 94 by vacuum extractor while in 13 cases a failed vacuum

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extraction was followed by forceps delivery. A group of 207 spontaneously delivered babies were included for comparison. In the total group of 413 newborns 48 showed retinal or pre-retinal macular haemorrhage in one or both eyes (11.6%). It has often been suspected that such macular haemorrhages could be the cause of an organic amblyopia possibly with a secondary strabismus due to poor vision. However, in spite of the considerable efforts directed towards the elucidation of amblyopia, follow-up examinations of such patients are rare.

As the children in the above mentioned study were now old enough for an evaluation of their visual functions and still not beyond the age where an amblyopia treatment might be successful, it was decided to re-investigate the children who had had perinatal macular haemorrhages.

Material and Methods

The study comprised 48 children born during the years 1969–71. Re-examination was undertaken of 39 children, 21 girls and 18 boys. In the remaining cases the family refused to attend for examination in spite of repeated requests.

It is thought that examination would have been accepted if an eye disorder had been present.

The examination comprised determination of visual acuity by means of E test types at a distance of 6 m. Refraction was determined by retinoscopy in cyclopentholate cycloplegia. Ocular position and motility were evaluated by inspection and by performing the cover test at near as well as distance fixation. Microstrabismus was investigated by the 4 dioptre base out prism test (Jampolsky). Fixation was studied by an ophthalmoscope with a central dark star and the possible presence of chorioretinal scarring was investigated by ophthalmoscopy. The sensory function was tested by the Schober test and Worth 4 dot test.

The examinations were time consuming but good cooperation with the child was achieved in almost all cases. Only in 1 case was examination impossible to perform due to lack of co-operation on the behalf of the child. The results of the examination of the remaining 38 children will be discussed.

The average age of the 38 children was 5⅔ years. There were originally 18 cases with macular haemorrhage in one eye and 20 cases with macular haemorrhage in both eyes. In 23 cases the haemorrhage persisted after one week, whereas they had re-absorbed in 15 cases. The method of delivery was by vacuum extraction in 21 cases, forceps in 6 cases, combined vacuum extraction and forceps in 3 cases and normal delivery in 8 cases.

Results

Visual acuity. In 35 out of the 38 patients (92.1%) the visual acuity was equal in both eyes and ranged from 0.67 in the youngest child (age 4 years 6 months) to 1.0 in the oldest child (age 6 years 4 months).

In the remaining 3 cases (7.9 %) a slight difference in visual acuity of between two to three lines was found. These included

a) Two cases of microstrabismus (5.3 %)

b) One case (2.6 %) with a normal muscular balance and no signs of strabismus

These cases will be presented

Case 1 A girl who had been delivered by a combination of vacuum extraction and forceps. Macular haemorrhages were observed in both eyes following delivery but had re-absorbed one week later. When the child was examined at the age of 5 years 3 months visual acuity was 1.0 OD and 0.7 OS. Cover test revealed an intermittent convergent strabismus of the left eye and the 4 d prism test confirmed the presence of a left sided suppression scotoma and a microstrabismus. Schober and W4L tests gave normal results. Cycloplegic retinoscopy +0.50 sph o.u.

Case 2 A girl delivered by vacuum extraction, with a single haemorrhage in the macula region of the right eye. This had disappeared one week later. The child was examined at the age of 5 years 3 months and visual acuity was 0.7 OD and 0.9 OS. There was no apparent strabismus but 4 d prism test revealed a central suppression scotoma on the right side confirming the presence of a microstrabismus. Schober and W4L gave normal results. Cycloplegic refraction +2.50 sph o.u.

Case 3 A boy delivered by vacuum extraction, with a macular haemorrhage on the left side which had disappeared after one week. Examination was performed at the age of 5 years 9 months. Visual acuity was 1.0 OD and 0.8 OS. Binocular balance, Schober and W4L were normal and there was no strabismus. Cycloplegic retinoscopy +1.0 sph o.u.

In the 3 patients with the reduced visual acuity two patients had a macular haemorrhage in one eye which later became amblyopic while the third patient had had a haemorrhage in both maculae. In all 3 cases the macular haemorrhage had disappeared by one week.

In none of the cases where the macular haemorrhage persisted after one week did amblyopia arise (23 cases). The series comprise 76 eyes, 58 with macular haemorrhage and 18 without. Of the 58 eyes with macular haemorrhage 3 had reduced visual acuity. Of the 18 eyes without macular haemorrhage all had normal visual acuity. This difference in occurrence of visual reduction when evaluated by a χ^2 test is not statistically significant ($\chi^2 = 0.97$, $P \sim 0.35$).

There was no question of any severe amblyopia necessitating occlusion treatment. In no case was any media opacity or anisometropia the cause of amblyopia.

Strabismus Two cases of microstrabismus as described above were discovered from the visual acuity and the 4 d prism test.

Sensory functions These were normal in all except for 3 patients who exhibited a mild heterophoria. There included a 10 Δ esophoria a 3 Δ esophoria and a 2 Δ exophoria as found with Schober's test These patients were otherwise normal with no difference in visual acuity and no strabismus Consequently the heterophoria was considered as being physiological

Ophthalmoscopy This was normal in all cases Fixation was central and there was no evidence of any abnormalities of the macula or fovea

Discussion

It has been stated and it is widely accepted that organic amblyopia may arise from disorganization of the foveal receptors by a macular haemorrhage occurring in the newborn The question of an amblyopia arising from malorientation of the foveal receptors has been examined by Enoch (1959) (receptor amblyopia) Burian in a discussion on the paper of Enoch put forward the suggestion that such a malalignment of receptors may be caused by a macular haemorrhage Sachsenweger (1965) estimated that about 10 % of amblyopia cases with strabismus may have an organic component and suggested that retinal haemorrhages play an important role in causing this This was also suggested by von Noorden (1967) in a paper on the origin of amblyopia Doege (1969) in a histological study of retinal haemorrhages found both subretinal and preretinal bleeding He stated that the haemorrhages in the macular region lasted longest and considered that the macula could be permanently damaged and organic amblyopia arise as a consequence

However as pointed out by von Noorden (1967) proof for this theory of organic amblyopia can only be provided if it can be shown that the incidence of amblyopia and strabismus is high in children who had macular haemorrhages at birth

While reports on retinal haemorrhages in the newborn are frequent reports on the incidence of macular haemorrhage are less frequent varying from 4 % to 12 % The incidence in our series was 11 6 %

What is more important is that follow up reports on patients with macular haemorrhages are seldom to be found There are in fact only three published series Bonamour (1949) examined 8 patients at the age of 10 years who had had macular haemorrhage at birth Seven of the patients were normal and the eighth patient had a slight amblyopia with an anisometropia (myopia) He concluded that both the long and short term prognosis of such haemorrhage were

good and did not result in macular damage amblyopia or strabismus Von Noorden and Khodadoust (1973) found 18 patients with macular haemorrhage out of 1000 newborns Of these only five were available for follow up examination at least four years later *All five patients were normal with no amblyopia* strabismus or macular changes They concluded that there was no relationship between neonatal macular haemorrhage and organic amblyopia

Schenk & Stangler Zuschrott (1974) examined 23 out of 42 children with neonatal macular haemorrhages aged between 3–7 years They found normal *ophthalmoscopy in all cases Visual acuity was normal in 15 cases undetermined* in 4 cases and in the remaining 3 cases was slightly reduced It was concluded that discrete organic damage to the macula could not be excluded in these cases. As far as binocular balance was concerned 14 were normal and 4 had reduced fusion There were two cases of microstrabismus convergens one case of accom *modative strabismus convergens and one case of strabismus divergens* They concluded that the sequelae of perinatal retinal haemorrhages should not be overestimated

In our series 35 out of 38 children with perinatal macular haemorrhage were normal and amongst these were several patients with severe macular haemorrhages which persisted after one week In the remaining three children there was a slight unilateral reduction of visual acuity and in two of these patients a microstrabismus could be demonstrated In no case was there any severe amblyopia as might be expected with a receptor amblyopia. Thus neither from the literature nor from the present series are there any grounds for supposing that perinatal macular haemorrhages produce organic amblyopia strabismus or macular scars

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ORBITAL PHLEBOGRAPHY

Technique and clinical applications

BY

GUDRUN BRISMAR and JAN BRISMAR

The technique for orbital phlebography is described and the phlebographic anatomy of the orbit and the skull base presented The possibilities and limitations of phlebography in the diagnosis of different intraorbital and ophthalmoneurological disorders is discussed and illustrated out of personal experiences from 200 cases

Key words orbit – orbital apex – skull base – orbit radiology – orbit phlebography – venous anatomy

In the investigation of suspected intraorbital disorders or of neuroophthalmological problems conventional neuroradiological techniques often prove insufficient. Skeletal films including tomography may demonstrate enlargement of the orbit destruction or sclerosis of its bony walls or of the skull base and sometimes intraorbital calcifications but in most cases give no diagnostic information Arteriography (preferably selective internal carotid and maxillary artery injections) in cases with well vascularized intraorbital tumours may provide information not only concerning the localization of the lesion but also on its nature. However demonstration of an avascular mass is more difficult as the course of intraorbital arteries is subject to large variations (Vignaud et al 1972) Furthermore arteriography as well as pneumoencephalography not sel

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dom fails to reveal lesions at the skull base There is thus a need for supplementary radiographic techniques Orbitography either with gas or with water soluable contrast media has been strongly advocated by several authors (Beisner 1969 Bertelsen 1962) and in the hands of experienced investigators offers valuable topographic information in cases with intraorbital tumours However the films can be difficult to interpret and furthermore serious complications have been reported in connection with these examinations whether performed with gas (Garcin & David 1966 Lombardi 1967) or with water soluable contrast media (Hansen 1956 Lombardi 1972) In the Second International Symposium on Orbital Disorders in Amsterdam 1972 though some investigators advocated orbitography with gas combined with tomography the general opinion was that this examination should be performed only on strict indications – i e on suspicion of a tumour confined to the intraorbital optic nerve

Orbital phlebography – i e examination of the intraorbital veins with contrast media – was introduced in 1951 by two French ophthalmologists Dejean and Boudet The examination was originally designed to diagnose intraorbital venous malformations but has proved to be superior to arteriography in the diagnosis of avascular intraorbital masses (Aron Rosa et al 1966 Lombardi & Passerini 1969 Lloyd 1970 Haye et al 1970 Hanafee 1972) and offers valuable information concerning the cavernous sinuses and the basal sinuses of the skull (Bregeat et al 1952 Piscol et al 1970 Lloyd 1972)

The aim of this report is

1) to discuss different techniques for orbital phlebography and to present in more detail our own technique

2) to demonstrate the normal venous anatomy of the orbit and skull base

3) to discuss the phlebographic findings in different disorders and to present some illustrative cases

4) to try to define the possibilities and limits of orbital phlebography and to establish the proper place for phlebography in the investigation of intraorbital and neuroophthalmological disorders

Different techniques for orbital phlebography

The technique originally presented by Dejean and Boudet consisted of puncture and cannulation of the surgically exposed angular vein Sometimes the draining facial veins were ligated in order to force the flow of contrast medium into the orbit under examination Thus only one orbit was examined though sometimes contrast medium passed over to the contralateral orbit if the collateral veins at the root of the nose were not ligated The examination could not be repeated as the angular vein was ligated at the end of the examination Yasargil (1957)

demonstrated that the angular vein could sometimes be percutaneously punctured Brovkina (1957) exposed the anterior facial vein and through this vein cannulated the angular vein

Yaşargil stated that, if puncture of the angular vein was unsuccessful percutaneous puncture of a frontal vein could be attempted Vritsios (1961) recommended the latter as the primary procedure The frontal vein injection permits bilateral filling of the intraorbital veins and a comparison between their course in the two orbits Vignaud & Clay (1969) used the same approach but substituted a teflon cannula with a metal mandrin for the earlier used scalp vein cannulas This modification provided not only a more stable intravasal position of the cannula but also the possibility of a more rapid injection of contrast medium and thus a better filling of the intraorbital veins

Hanafee et al demonstrated that catheterization of the inferior petrosal sinus after percutaneous puncture of the jugular vein could be used to study the basilar sinuses of the skull (1965) and also to evaluate the intraorbital veins (1968) Takahashi & Tanaka (1971) demonstrated that the inferior petrosal sinus could as well be catheterized from the femoral veins

During the last few years almost all investigators have turned to percutaneous frontal vein puncture as the standard method for examination of not only the intraorbital veins but also the veins at the base of the skull However in cases with occlusion of intraorbital veins a posterior approach i e transjugular inferior petrosal sinus catheterization has to be used in order to delineate the posterior limit of the occlusion This latter technique can also be used when a frontal vein puncture attempt is unsuccessful

Description of Technique Used

The technique for orbital phlebography used has been described in detail elsewhere (Brismar 1974a) Special preparation of the adult patient before examination is not needed thus the examination can be performed on an out patient basis In children below the age of 12–14 years general anesthesia is used

For puncture the patient is placed in the supine hanging head position and a tourniquet is placed across the forehead supraorbitally in order to distend the frontal veins A frontal vein is entered percutaneously using a disposable teflon cannula with a metal mandrin (inner diameter of cannula 1 05 mm) Three exposures are made in each of five different projections (Fig 1) one frontal view with the beam angulated 15 cranad from the orbito meatal line one semi axial view with the beam directed 45 cranad one basal view with the beam perpendicular to the skull base one straight lateral view and one

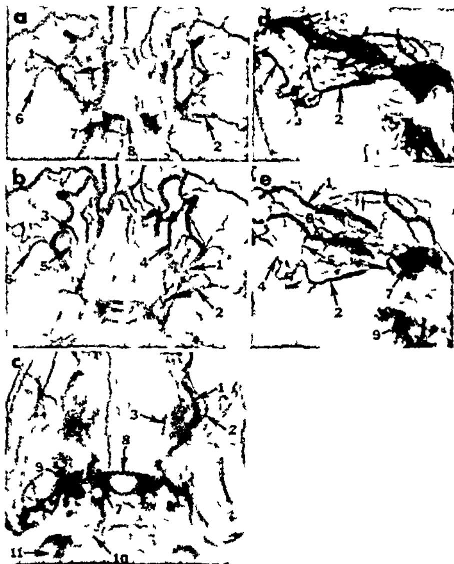


Fig. 1

Orbital phlebography normal case. Projections routinely used a) a.p. b) s… axial c) axial d) straight lateral and e) oblique lateral views. Superior (1) inferior ( ) and medial (3) ophthalmic veins as well as anterior (4) medial (5) and lateral (6) collateral veins filled. Cavernous sinuses ( ) interconnected through intercavernous sinuses (8) drain laterally through foramen ovale to pterygoid plexus (9) and posteriorly through inferior petrosal sinus (10) to internal jugular vein (11)

oblique lateral view with one orbit projected above the other For each series of exposures 10 ml of contrast medium (Isopaque cerebral Nyco Norway) is injected over 1–2 seconds the injection starts immediately after exposure of the first film in the series and the films are exposed at 1 second intervals During the examination the facial veins above the injection site are compressed by a tourniquet applied around the head furthermore the patient digitally compresses his angular veins and if necessary also his supraorbital veins in order to direct the flow of medium into the orbits (Fig 2)

The technique for inferior petrosal sinuography has been described in detail by Hanafee et al (1965 1968) The internal jugular vein is percutaneously punctured a thin catheter is introduced and the inferior petrosal sinus catheterized during fluoroscopy Injection of contrast medium and exposure techniques are the same as described above

Subtraction is routinely employed

Puncture failures and complications

In the hands of a trained investigator the rate of unsuccessful attempts at puncture of a frontal vein amounts to a few per cent (Brismar 1974a) The technique for orbital phlebography is simple to learn and the investigation could be per

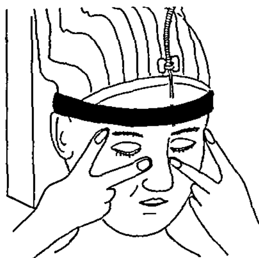


Fig 2

Orbital phlebography position of patient and technique for compression Tourniquet occludes frontal veins above injection site while patient with his 2nd and 3rd fingers bilaterally compresses supraorbital and angular veins

formed at any radiological department No serious complications have yet been published in association with orbital phlebography performed with a proper technique (Brismar et al 1976) Sometimes there is a rupture of small facial veins with the development of a hematoma In one of our cases (Brismar et al 1976) with a generalized cerebral vasculitis rupture of an intraorbital vein was observed No sequelae developed

Inferior petrosal sinus phlebography is for anatomical reasons (i e anomalous course of the inferior petrosal sinus) unsuccessful in about 25% of the cases (Hanafee et al 1968) *These investigators in a material of 100 examinations* encountered 3 complications – one patient developed a partial lateral medullary syndrome and in 2 patients contrast medium extravasated extradurally In all cases the symptoms were transitory In one case in the present series (Brismar et al 1976) the symptoms and signs from a carotid cavernous fistula increased after inferior petrosal sinus phlebography indicating a dilatation of the fistula.

Anatomy

Detailed anatomical studies of the intraorbital veins have been performed by several authors (e g Seseman 1869 Gurwitch 1883 Henry 1959) The phlebographic anatomy of these veins as well as of the basal sinuses of the skull has

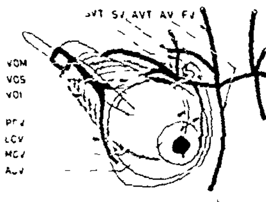


Fig 3

Intraorbital veins and veins in the vicinity of the orbit FV frontal vein SV supraorbital vein AV angular vein SVT tributary to VOS from SV AVT tributary to VOS from AV VOS VOM and VOI superior medial and inferior ophthalmic veins ACV MCV LCV and PCV anterior medial lateral and posterior collateral veins

been presented in detail by Brismar 1974b c 1975) In the following description the nomenclature used in these latter publications will be followed

The intraorbital veins (Figs 1 3)

The intraorbital veins can be divided into two groups – the ophthalmic veins and the collateral veins The ophthalmic veins (superior medial and inferior ophthalmic veins) have an essentially antero posterior course connecting the anterior parts of the orbit and the facial veins with the cavernous sinus through the superior orbital fissure The collateral veins (anterior medial lateral and posterior collateral veins) have an es entially caudocranial course and form connections between the superior ophthalmic vein and veins at the orbital floor

The superior ophthalmic vein is the main intraorbital vein and with a proper phlebographic technique can always be demonstrated in normal cases It is connected to all other intraorbital veins either directly or through collateral veins It is formed close behind the pulley of the superior oblique muscle by the junction of two branches one from the angular vein passing along the medial orbital wall and inferior to the pulley and one from the supraorbital vein passing through the supraorbital incisure and superior to the pulley After making a loop deep to the pulley the superior ophthalmic vein courses laterally backwards passing below the superior rectus muscle Having reached the lateral aspect of this muscle the vein makes a turn (the lateral deflexion point) and follows the lateral border of the muscle backwards and medially passing through the superior orbital fissure and emptying into the cavernous sinus The course of the superior ophthalmic vein is relatively constant and usually a good sym metry can be expected when comparing the right and left orbits However assymetries may exist especially when part of the superior ophthalmic vein is re duplicated Furthermore the loop formed by the anterior part of the vein (before it enters the muscle cone) is subject to considerable variations The diameter of the superior ophthalmic vein is maximal in the midpart of the orbit and constantly considerably decreases as the vein passes through the superior orbital fissure The average maximum diameter of the vein (measured on lateral films) amounts to 3 5 mm while the average minimum diameter during the passage through the fissure amounts to 1 8 mm The diameter of the vein is subject to large variations between the two sides as well as between individuals

The medial ophthalmic vein (filled in 1/3 of orbits) originates from the anterior part of the superior ophthalmic vein or from its angular tributary branch It passes backwards along the upper part of the medial orbital wall and in the posterior part of the orbit descends to enter the cavernous sinus below the superior ophthalmic vein

Results and Discussion

Demonstration of intraorbital venous malformations such as varicosities, venous networks and hemangiomas with large venous components is the most obvious use of orbital phlebography and such lesions are presented in most reports on orbital phlebography. However, the early investigators used too narrow limits for the normal variations in diameter of the superior ophthalmic vein (Offret & Aron Rosa 1965) and overinterpreted "varicose" veins. As described by Lloyd et al. (1971) the majority of orbital hemangiomas will at phlebography present as avascular tumors. In some of these cases arteriography will demonstrate the lesion (Fig. 4). Only one venous malformation was found in the present series (Fig. 5).

The dislocation of veins that is produced by an intraorbital tumour large enough to give exophthalmos was in most cases found to give enough information concerning the location and extension of the tumour to permit needle biopsy and selection of the proper surgical approach. In some cases pathological veins

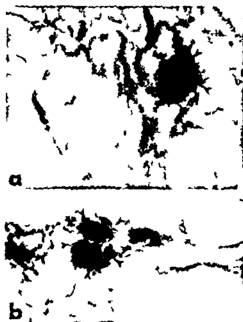


Fig. 5

Patient with left sided buccal and subcutaneous temporal venous malformation [illegible] vision in left eye when bending forward. a) b) orbital phlebography, semiaxial and lateral projections, demonstrates venous malformation (arrow head) in the [illegible]

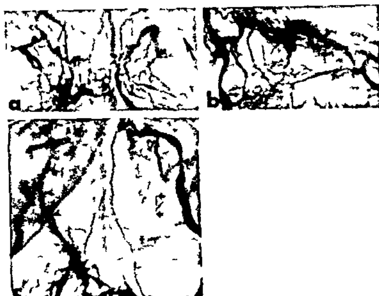


Fig 6

Left sided meningioma growing in the orbital roof causing left sided proptosis a) b) c) orbital phlebography a p lateral and axial views While right superior opthalmic vein (arrow heads) has normal course, left (short arrows) is dislocated downwards medially and compressed Filling of abnormal veins (long arrow)

may be demonstrated (Figs 6 7) but usually the tumour presents as an avascular expanding mass (Fig 8) Tumours situated in the apex of the orbit because of the limited space available will produce early symptoms due to compression of adjacent nerves (Lloyd 1972 Hanafee 1972) The superior ophthalmic vein will be compressed at the same time permitting an early phlebographic diagnosis (Fig 9) However in these cases the only phlebographic sign will often be occlusion of the superior ophthalmic vein without any evident dislocation of veins Exactly the same phlebographic appearance may be caused by a primary intraorbital venous thrombosis and also by a carcinoma of the epipharynx or *the skull base that is occluding the superior ophthalmic vein or the cavernous* sinus if combined with a secondary thrombosis propagating into the intra orbital veins Because the clinical pictures may also be identical the differential diagnosis is often very difficult Sometimes in spite of extensive clinical and radiological investigations including multiple epipharyngoscopies with biopsy the definite diagnosis has to wait until further symptoms or signs develop (Bris mar et al 1975)

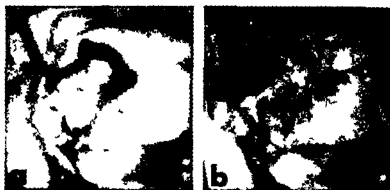


Fig 10

Thirty nine year old man with periods of unilateral proptosis for a few years. No endocrine dysfunction. Interpreted as inflammatory condition. Orbital phlebography (a. p. views of left orbit without compression) a) when having only right sided symptoms b) half a year later when symptoms and signs instead affected the left eye. Left orbit is normal at the first examination, at the second examination the diameter of the superior ophthalmic vein has decreased and several small irregular inflammatory veins are filled

these venous structures. Furthermore as the cavernous sinuses form the lateral borders of the pituitary fossa orbital phlebography by demonstrating lateral dislocation of the cavernous sinuses will give valuable information concerning the lateral extension of the pituitary tumours (Fig. 11)



Fig 11

Pituitary adenoma. Orbital phlebography axial view. Tumour compresses and dislocates cavernous sinuses (arrow heads, most pronounced on left side

Conclusions

1 Orbital phlebography performed by percutaneous injection of a frontal vein is a benign procedure well suited for use on out patients

2 The examination offers valuable information not only in cases with primary venous disorders but also in patients with intraorbital tumours or with tumours at the skull base It should therefore be used on liberal indications in patients with orbital symptoms or with ophthalmoneurological symptoms possibly attributed to the skull base or cavernous area. In cases with posterior occlusion of the superior ophthalmic vein epipharyngeal or skull base malignancy must be excluded before the diagnosis of thrombosis is established

3 As carotid arteriography by demonstrating the arteries and capillaries gives different information the two methods are complementary A negative phlebography alone must thus not be allowed to exclude carotid angiography in cases with a suspected tumor – neither should a negative arteriography alone exclude phlebography

4 The information achieved by phlebography and arteriography in combination has proven sufficient to obviate the need for orbitography except for the exclusion of small optic nerve tumors

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TRAUMATIC HYPHAEMA TREATED WITH THE ANTIFIBRINOLYTIC DRUG TRANEXAMIC ACID

BY

THORKILD BRAMSEN

During the year 1975 (Jan. 1st–Dec. 31st) 72 patients consecutively admitted to the eye department of Århus Kommunehospital with traumatic hyphaema were treated with the antifibrinolytic drug tranexamic acid. Secondary haemorrhage occurred in one case. This incidence of secondary haemorrhage (1.4%) seems to be the lowest on record.
A group of patients from the period 1965–19[illegible] treated identically with the exception of the tranexamic acid were selected for comparison. This group of 135 patients included 9 cases (6.7%) with a secondary haemorrhage. The difference between these two groups is statistically significant ($P < 0.05$).

Key words: traumatic hyphaema – secondary haemorrhage – fibrinolytic therapy – tranexamic acid

Secondary haemorrhage is the most serious complication of traumatic hyphaema and previous papers on hyphaema are mainly concerned with this complication. The varying percentages of secondary haemorrhage recorded in the literature can only be understood if the severity of the lesions and the treatment vary. Morris (1960) reported 1% of secondary haemorrhage with

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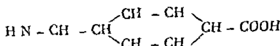


Fig 1
Trans 4 aminomethylcyclohexanecarboxylic acid (tranexamic acid)

conservative treatment while Gregersen (1962) found only 5–6 % Öhrstrom (1972) found 2 4 % when the patients received topical atropin and steroid Bengtsson & Ehinger (1975) reported 5 3 % with complete bed rest without topical medication A much higher incidence is reported in American papers (up to 40 %)

In 1972 Öhrstrom described that laceration of the vessels at the contusion site is immediately followed by vasoconstriction and subsequently clot formation which plugs the vessel The trauma is followed by an inflammatory process which increases the permeability of the blood aqueous barrier and permits the passage of plasma proteins including plasminogen into the anterior chamber The trauma also results in liberation of tissue activators which convert plasminogen into plasmin resulting in fibrinolysis and decomposition of the primary clot In this way a secondary bleeding may occur In 1974 Watkins described the beneficial effect of a fibrinolytic inhibitor (ε amino caproic acid) on recurrent hyphaema in four patients The series of Gregersen (1962) showed that secondary haemorrhages usually occur between the second and fifth day following the trauma which suggests the possibility of a fibrinolytic bleeding If the secondary haemorrhage is a fibrinolytic bleeding theoretically it might be avoided by an inhibition of the fibrinolysis

Tranexamic acid (Cyklokapron®) (Fig 1) is an antifibrinolytic drug which inhibits the conversion of plasminogen to plasmin and thus prevents the decomposition of fibrin to fibrin split products (Fig 2)

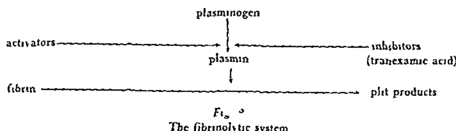


Fig 2
The fibrinolytic system

Material

The material comprised 7[illegible] patients with traumatic hyphaema consecutively admitted to the Department of Ophthalmology during the period January 1st to December 31st 19[illegible]. Excluded from the material were those patients with ocular contusion without any hyphaema, patients with only a haemorrhagic aqueous flare and patients admitted with a secondary haemorrhage. All cases with perforating lesions were also excluded. (4 patients with a haemorrhagic aqueous flare and 1 patient admitted with a secondary haemorrhage were treated with tranexamic acid without any recurrence of haemorrhage.) The [illegible]2 patients comprised 60 males (average age [illegible]0.[illegible] years, range [illegible] months to 61 years) and 1[illegible] females (average age [illegible]0.1 years, range 1 to [illegible]5 years). The patients were usually admitted either from the casualty department or from a general practitioner. Only a few patients were referred by an ophthalmologist.

The associated ocular lesions can be seen from Table I.

Methods

The treatment consisted of complete bed rest for five days, stenopaeic spectacles and peroral *tranexamic acid* (Cyklokapron®). The dose was [illegible] mg/kg body weight three times daily for 6 days. Tranexamic acid is administered in tabletform. The patients were discharged on the fifth day. Mydriatics and topical steroids were not used. Acetazolamide was given if a rise in intraocular pressure (> 30 mmHg) developed. Biomicroscopy, ophthalmoscopy, measurement of intraocular tension and determination of visual acuity were performed on the 5th and 1[illegible]th day.

Table I

Lesions associated with traumatic hyphaema.

	No. of patients
Subconjunctival haematoma	6
Corneal erosion	14
Pupillary changes	3[illegible]
Iridodialysis	[illegible]
Increased intraocular tension	5
Traumatic cataract	1
Retinal haemorrhage	
Central retinal oedema	[illegible]
Choroidal rupture	1
No associated lesions	5
No. of patients	[illegible]

Table II
A comparison between the two groups treated with and without tranexamic acid

Material	1975 group	1965–68 group
No of patients	72	135
Males	60	104
Females	12 (16 6 %)	31 (22 9 %)
Average age males (years)	20 8	21 5
Average age females (years)	20 1	15 6
Average stay (days)	5 0	4 8

As mentioned previously it is difficult to compare the results with those from other eye departments because of possible variation in criteria for admission. The patients admitted to our department during the period 1965–68 will therefore be used for comparison These patients were selected retrospectively and only those treated with complete bed rest and stenopaeic spectacles alone were accepted. The only difference between this group and the 1975 series is the treatment with tranexamic acid In the period 1969–19 4 the treatment was individualized to such a degree that no reasonable groups could be formed for comparison. The selected group consisted of 104 males with an average age of 21 5 years (2–58) and 31 females with an average age of 15 6 years (7–35) The frequency of secondary haemorrhage in this group was 6 7 % which is similar to the frequency found in another Danish series (Gregersen 1962) In Table II the two groups are compared

Results

Of the patients admitted in 1975 a secondary haemorrhages occurred in 1 (1 4 %)

Case report

A 12 year old boy (patient No 52) was admitted 36 h after the eye trauma On admission 2/3 of the anterior chamber was filled with blood The treatment consisted of complete bed rest stenopaeic spectacles and tranexamic acid The intraocular tension

was 32 mmHg and acetazolamide was given 2 h after admission (58 h after the trauma) the eye became painful and a new small haemorrhage was visible in the upper part of the anterior chamber The intraocular tension was at that time — mmHg Tranexamic acid was administered for six days after the occurrence of the secondary haemorrhage and the patient was discharged after five days of treatment. One week after discharge the visual acuity was 1 0 the hypahaema had disappeared there was no iritis ophthalmoscopy was normal and gonioscopy of the lower angle showed a small goniosynechia.

Follow up examination on the 12th day after the trauma showed visual acuities as illustrated in Table III No cases of iritis or of increased intra ocular tension were found

The primary clot remains in the anterior chamber during the administration of tranexamic acid and this might possibly result in goniosynechias Tønjum (1966) found lesions of the chamber angle in 94 3 % following traumatic hyphaema The contusious angles have not been regularly studied in our material but patients over 10 years of age were examined with special reference to goniosynechias at the site of the primary clot Synechias were found in 2 out of 57 patients One of these was the patient with the secondary haemorrhage

In the group of 135 patients from 1965–68 secondary haemorrhages occurred in 9 (6 7 %) In all cases recurrence of the bleeding occurred from the 2nd to 4th day

It was not possible to make any comparison between the late results in the two groups because a regular follow up examination of the group from 1965–68 was not undertaken

A comparison between the two groups may be made as follows the risk of secondary haemorrhage in the 1965–68 group was 0 067 (6 7 %) a figure

Table III

Visual acuity of 2 tranexamic treated patients with hyphaema 1 days after the trauma

Visual acuity	No of patients
1 0	5
0 5–0 9	8
0 3–0 4	3
0 1–0 3	4
< 0 1	0

similar to that of several other series e g Gregersen (1962) The probability of not having a secondary haemorrhage is therefore a priori 0 933 Using probability calculus the possibility of finding 72 cases without a secondary haemorrhage is

$$(0\ 933) = 0\ 00678$$

and the possibility of having 71 cases without secondary haemorrhage and 1 case with haemorrhages is

$$(0\ 933)^{1} \quad \binom{7}{71} \quad 0\ 067 = 0\ 03508$$

Therefore the probability of having by chance the observed or a still better result is

$$0\ 00678 + 0\ 03508 = 0\ 04186 \sim 4\ 2\ \%$$

We may therefore say that the probability of an effect of the given treatment is 95 8 %

Discussion

The treatment is based on the hypothesis that a secondary haemorrhage is due to a fibrinolytic bleeding The fibrinolytic activity in the anterior chamber in connection with hyphaema has not been examined However the fact that the clot remains in the anterior chamber as long as the antifibrinolytic drug tranexamic acid is administered suggests the presence of a fibrinolytic activity in the anterior chamber

In order to verify the effect of tranexamic acid on the incidence of secondary haemorrhages a double blind study would be desirable However this would be difficult to perform in practice because a haemorrhage which has not disappeared before the effect of tranexamic acid has set in will remain as a dark clot in the anterior chamber until the discontinuation of tranexamic acid In most of the cases it would therefore be obvious that tranexamic acid had been used

The material is small but it appears that the prognosis of hyphaema is better when tranexamic acid is used 1 4 % is the lowest reported incidence of secondary haemorrhage and when compared with similarly treated series from our department with the exception of the tranexamic acid a statistically significant difference is found

The only recorded side effect in our series was an increased peristaltic motion and this has not resulted in any discontinuation of treatment A family

suffering from hereditary angioneurotic oedeme treated with tranexamic acid for four years with the same dosage as used in hyphaema (Zachariae 1975) has been examined and no ocular pathology found There were no other side effects

As from January 1st 1976 patients with hyphaema admitted to our department are being treated solely with tranexamic acid Bed rest and stenopaeic spectacles have been discontinued If this proves satisfactory an out patient treatment will be considered

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Runyan Thomas E Concussive and penetrating injuries of the globe and optic nerve The C V Mosby Company Saint Louis 1975 pages 221 $ 31 00

The scope of the text has been confined to concussive and penetrating injuries of the eye ball and the optic nerve The effects of radiation and the damaging effects of various chemical agents are not included Reconstructive surgery of the lids and adnexa is not treated.

The material is arranged anatomically Each chapter is preceded by a brief anatomical and physiological review The various types of lesions are presented. The procedures to be followed in examination and treatment are discussed on the basis of recent reports in the literature. The author does not as a rule present any treatments of choice which may be considered both the strength and the weakness of the book No discussion of proper surgical technique is given.

All illustrations are drawings made by the author no photographs are included The text is fairly concise and the book may be recommended to students of ophthalmology

Niels Ehlers

W Boke & M H Lunt Ocular immune responses Modern problems in ophthalmology volume 16 S Karger Basel 1976 SFr 99/DM 94

The first international symposium on immunology and immunopathology of the eye was held in Strassbourg 1974 The present volume of the series Modern problems in ophthalmology contains the proceedings of the symposium

The papers are grouped under various headings – aspects of autoimmune mechanisms in uveitis – various problems of ocular immunopathology – viral and parasitic immunopathology – immunological tests in uveitis – immunosuppressive therapy These sections are followed by discussion which can be highly recommended to the reader All papers are brief concise and followed by a summary

The book will be found as vol 16 of Mod probl Ophthal in many clinical departments and laboratories It can be highly recommended and should be mandatory to those engaged in research in the field of ocular immunology

Niels Ehlers

François J Ocular Manifestations of Inborn Errors of Carbohydrate and Lipid Metabolism Bibl Ophthalmologica 84 S Karger Basel 1975 D kr 945 00

Professor J François has recently published surveys of amino acidopathies and mucopolysaccharidoses in ophthalmology and the above mentioned book should be regarded as the third part of this trilogy It comprises only the metabolic disorders associated with ocular manifestations and the discussion of these is dimensioned in such a way that the more common diseases are treated at greather length than those which have been reported only in a few patients Moreover as might be expected the diseases on which

François has personally reported are treated more critically than those of which he has had only second hand information through the literature.

The book begins with a discussion of inborn errors of carbohydrate metabolism. The main emphasis is on galactosaemia a disease that ophthalmologists should bear in mind when seeing mentally retarded children with congenital cataract Other disorders of carbohydrate metabolism are also mentioned

Of the lipidoses the gangliosidoses Niemann Pick s and Gaucher s diseases are fully described and here as throughout the book extremely instructive and beautiful illustrations accompany the text Disorders in which the metabolic background has not yet been established are mentioned such as Batten s (Spielmeyer Vogt s) disease and Santavuori s newly delineated infantile ceroid lipo fuscinosis There is a chapter on Pelizaeus Merzbacher s disease where the genetic heterogeneity is hardly mentioned and where the metabolic errors have not been estabished Informative surveys are given of the rarer lipidoses such as Krabbe s Farber s Wolman s Bassen Kornzweig s Tangier s and Hooft s diseases and there are detailed descriptions of Fabry s and Refsum s diseases

I find that the last chapter on mucolipidoses is particularly lucid and informative. These are fairly recently delineated syndromes with rather similar clinical features that resemble those seen in some of the mucopolysaccharidoses The patients however do not excrete mucopolysaccharide It is of great value to have in this book an ophthalmological approach to the differential diagnoses

The aforementioned two articles and this publication together constitute a comprehensive compendium of the rapidly developing field of metabolic errors in ophthalmology It is easily read mainly because biochemical explanations are excluded but where such would seem important for a full understanding the references which are plentiful and impressively up to date will easily fill the need

The book is particularly recommendable for postgraduate training and would be very useful as a basis for small study groups

Mette Warburg

XXIIIrd International Congress of Ophthalmology

will be held in Kyoto Japan from the 14th of May 1978 to the 21st

The main themas of the Congress will be The pigmentary epithelium (Clinical aspects Biochemical aspects Electromicroscopy) and Ocular Immunology (General considerations Uveitis and aqueous fluid, Cornea and lens)

International Symposium on Computer Assisted Tomography at the National Institutes of Health

An international symposium on Computer Assisted Tomography in Nontumoral Diseases of the Brain Spinal Cord and Eye sponsored by the National Institute of Neurological and Communicative Disorders and Stroke is announced The meeting will be held at the Clinical Center on the campus of the National Institutes of Health, Bethesda Maryland USA October 12–15 1976 under the chairmanship of Giovanni Di Chiro Mailing address Giovanni Di Chiro M.D., National Institutes of Health Section on Neuroradiology Clinical Center Room 2D13 Bethesda, Maryland 20014

Second International Congress of Eye Research

will be held in Jerusalem Israel September 12–17 1976 Secretariat 7 Leteris Street P O Box 16271 Tel Aviv Israel

Congressus XXIII Ophthalmicorum Septentrionalium

XXIII Nordiske Oftalmolog møde will be held in Copenhagen May 25–28 1977 Secretariat Department of Ophthalmology Rigshospitalet 9 Blegdamsvej DK 2100 Copenhagen Ø Denmark

The European Ophthalmic Pathology Society

held its 14th Annual Meeting in Oslo Norway June 3–6 1975

The meeting was perfectly organised by Professor and Mrs K. Arnesen The scientific sessions were held at the University of Oslo Institute of Preclinical Odontology Dr S Ry Andersen Denmark was elected President and Dr O A Jensen, Denmark Corresponding secretary

The Johns Hopkins University
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ON THE INTERPRETATION OF DEPTH DEPENDENT LIGHT SCATTERING MEASUREMENTS IN NORMAL CORNEAS

BY

RICHARD A FARRELL and RUSSELL L McCALLY

In recent studies other investigators have presented traces of light scattering versus depth into the cornea The present investigation de monstrates that these traces do not measure the actual light scatter in tensity and that a proper interpretation of such traces shows that most of the scattering is from within the stroma

Key words corneal light scattering – stroma

In an interesting article published in this Journal Lindstrom Feuk & Teng roth (1973) showed traces of corneal scatter intensity versus depth into the normal rabbit cornea and concluded that From the results presented it is evident that the main contribution to the *integrated* scattered intenity comes from regions close to the limiting layers i e the epithelium and endothelium Their trace is reproduced in Fig 1 (which is Fig 8 of their paper) and the

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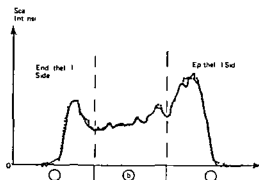


Fig 1
Traces of scatter amplitude vs depth into the cornea measured by Lindstrom et al (1973)

purpose of this brief report is to demonstrate that this trace actually suggests that most of the scattering comes from within the stroma Such an interpretation follows from taking into proper account the distortions introduced into the traces by the spatial response function of (i e. the finite resolution of) the measuring apparatus The fact that in Fig 1 the depth of the region marked epithelial side is approximately seventy per cent of the depth of the stromal region (between the two dashed lines) is an obvious manifestation of a lack of resolving power (The depth of the epithelium is only about one tenth the stromal depth)

The correction factors needed to interpret their trace depend both on the spatial response function of the apparatus and on the characteristics of the scattering medium The concepts of a spatial response function are briefly reviewed and used to analyze several simple examples The extensions required to analyze the experiments of Lindstrom et al (1973) are developed and the results show that at the scattering angle used by them more than seventy per cent of the scattering originates from within the stroma More detailed studies of the interpretation of angular light scattering measurements are reported in McCally & Farrell (in preparation) where the present analysis is extended to account for effects due to refraction of light at the curved corneal surfaces as well as for effects due to attenuation of the incident and scattered beams (These effects are secondary in importance compared to the distortions discussed in the present analysis) McCally & Farrell (1976) made measurements at a wide range of scattering angles (between 20°–145°) and demonstrated that most of the scattering occurs within the stroma for all the scattering angles studied

Methods

Spatial response functions

The detector senses the scattering through its spatial response (transfer) function R(x–x') which gives the value of the signal measured by the detector located at x due to a point source of unit strength located at x' The response to a set of point sources is simply the sum of the contributions from the individual sources In the case of a continuously distributed source the sum becomes an integral and the measured signal J(x) is the convolution of the actual distributed scatter intensity I(x') with the spatial response function i e

$$J(x) = \int dx' \; R(x-x')I(x') \tag{1}$$

For an ideal detector the response function would be a Dirac delta function (Dirac 1947) and in that case one finds J(x) = I(x) However diffraction and the finite size (field stop) of the detector do not allow one to attain this limit For real detectors ideal behaviour will be achieved only if the actual scatter intensity does not change appreciably over distances comparable to the width of the response function (i e over a few resolution widths) in which case one finds

$$J(x) \approx I(x) \int dx' \; R(x-x') = \text{const} \; I(x) \tag{2}$$

In this special case the integrated scatter intensity (measured signal) is proportional to the actual scatter intensity and the detector is ideal in the sense that the traces give a scaled representation of the actual scattering (Our use of the term integrated scatter intensity here and in the following derives from the integral relationship of Eq (1)) Unfortunately Eq (2) is not generally valid for the experiments of Lindstrom et al although it does hold within the central stromal region for their experiments

In general the response function depends on three space variables but for a microscope system in which all the scattering occurs within the depth of focus one can assume the response function is independent of the coordinate along the detector axis Also the scattering cross section with the cornea depends only on depth into the cornea (i e the cross section is constant at a given depth) and in a typical scattering experiment the vertical height of the illuminating slit of light is large compared to the effective height of the detector Under these conditions the detector can be characterized by its response to a tall very thin slit of light where the slit is in a plane normal to the detector axis and the long axis of the slit is in the vertical direction Lindstrom (1973) measured the slit response function[1] for the detector em

[1] The slit response function can also be obtained by integrating the point response function over the volume of the slit where the fictitious depth of the slit is arbitrary provided it is small compared to the depth of focus of the microscope

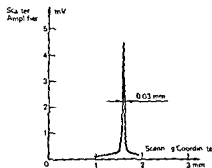


Fig 2
The slit response function of the detector used by Lindstrom et al (1973) – taken from Lindstrom (1973)

ployed in Lindstrom et al (1973) by recording the signal while moving a slit source past the detector The resultant response function (cf Fig 2) is well represented by an isosceles triangle whose full width at half maximum is $\sim 30\ \mu m$ Thus the non zero resolution width of the detector has distorted the actual intensity distribution which is a narrow slit into an integrated intensity which is a broad triangle

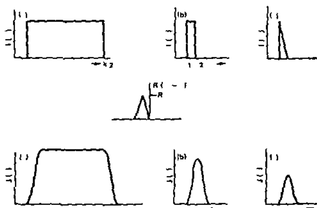


Fig 3
Distortions introduced into three simple intensity distributions by the resolution width of the detector The measured signal J(x) is plotted against the position of the leading edge of the detector x Here the right hand edge of the triangular response function is used as the leading edge of the detector

The effects of this distortion on other simple intensity distributions are shown in Figs 3a–3c) The approximation of the response function as an isosceles triangle of height R_0 and of full width at the base (2γ) is shown on the middle line The rectangular shaped intensity in Fig 3a is a constant I within the interval of $x_1 \leq x \leq x_2$ and is zero outside this interval Since $(x_2 - x_1)$ is large compared to (2γ) the detector is ideal for the interior region (regions near $x = (x_1 + x_2)/2$) in that the intergrated intensity is constant however the sharp edges of the distribution are blurred in the integrated intensity The intensity in Fig 3b is also rectangular but in this case $(x_1 - x_2) \sim \gamma$ The blurring of the sharp edges is again present and in addition the region in which the detector acts in an ideal manner is absent Similar results are found for the triangular distribution of intensity shown in Fig 3c These examples illustrate the general result that the integrated scatter intensity will give a reasonable representation of the actual intensity in regions where the actual scatter intensity is constant over a distance large compared to the resolution width but will give a severely distorted representation of features which have characteristic dimensions comparable to/or smaller than the resolution width Thus the traces of Lindstrom et al (1973) are expected to give a valid representation of corneal scattering only within the middle portion of the stromal region In the next section correction factors are developed which enable one to deduce the fraction of the scatter intensity which is contributed by the stroma from the measured traces

Results

Application to corneal scattering

The use of light scattering to characterize the normal cornea forms the basis of slit lamp examinations When the beam is incident normal to the corneal surface and the scattered light is viewed in lateral directions (scattering angles close to 90°) the notable features are the non scattering epithelium bounded by two narrow bright bands the stroma in which the scattering is relatively uniform but less intense than in the two bright bands and a bright band in the region of the endothelium (Duke Elder & Wybar 1967) A schematic representation of this distribution of scattered intensity is displayed in Fig 4a and Fig 4d depicts the signal which would be measured if this distribution were scanned past a detector with the triangular response function of 30 microns full width at half maximum (FWHM) shown in Fig 4b (The resolution width (FWHM) of the detector used by Lindstrom et al (1974) was ~ 30 microns (cf Fig 2)) The distribution in Fig 4a can be decomposed into

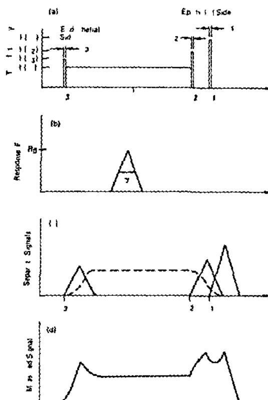


Fig 4

A schematic representation of the depth dependence of corneal scattering intensity is given in (a) The triangular spatial response function of the detector is shown in (b) and (d) shows the total signal which is measured when the distribution in (a) is scanned past this detector The diagram in (c) shows each of the components which are summed to comprise the total signal

three slit distributions of intensity (at positions x_1 x and x_3) and a rectangular distribution of intensity (in Region s) Fig 4c shows that the measured signal is a composite of the distorted signal from the individual slit and rectangular distributions (compare Figs 2 and 3a) Under these conditions the two bright bands which bound the epithelium give rise to the two peaks in the epithelial region of the measured signal The apparent broadening of the epithelial and endothelial *regions are obvious manifestations of distortions introduced by the* finite width of the *detector* response function

The experiments of Lindstrom et al (1973) were made at a scattering angle of 135° At scattering angles other than 90° the finite width w of the incident beam introduces futher distortions into the measured signal In their optical

configuration they collected light along the normal to the corneal surface and had the incident beam directed at 45° to the normal This scattering configuration is schematized in Fig 5a The shading in the sketch represents the scattered intensity in the illuminated portion of the cornea The qualitative

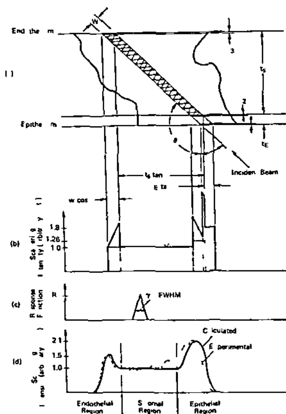


Fig 5

The finite width w of the incident beam causes the intensity distribution to be distorted when the sample is viewed at an angle Θ Here the true intensity is represented at the top of the figure and the distortion introduced by the width of the beam is represented by the projection in the center of the figure The amplitudes of the various regions are also adjusted by appropriate trigonometric factors to account for the projection. The final result is obtained by scanning this distribution with the slit response function of the detector and is shown at the bottom of the figure The solid line is the calculated distribution using the parameters given by Lindstrom et al (1973) and the dotted line is their measured trace

features of the variation of intensity with depth into the cornea in this example are the same as those described in the previous paragraph and illustrated in Fig 4a In the illustrative calculation to follow 60 % of the total scatter is assumed to come from the mid stroma 12 % from the band in the anterior stromal region[*] 18 % from the band at the front surface of the epithelium and 10 % from the band near the endothelium Thus some 72 % of the total scatter is assumed to emanate from within the stromal region If this distribution were viewed at an angle as in the experiment of Lindstrom et al (1973) one would see a distorted picture of the actual distribution as given by the geometric projection in Fig 5b This distortion of the true distribution is related to the finite width of the incident beam the stromal thickness t and the epithelial thickness t_E (The further distortions introduced by the finite thickness of the bright bands and the non uniform intensity across the incident beam are neglected in this analysis) The thin bands transform into rectangles and the rectangular stromal intensity transforms into three parts two triangular distributions and a rectangular distribution In Fig 5b $\Theta = 135°$ and $w \approx 35$ μm (which are the values quoted by Lindstrom et al (1973)) The values of stromal and epithelial thickness are respectively 340 μm and 40 μm which are typical of rabbit corneas The sharp peak in the epithelial region of Fig 5b results from the overlap in the projections of the two bright bands bounding the epithelium

The geometric projection in Fig 5b is the signal one would measure with an ideal detector however as discussed in the preceeding section the detector employed by Lindstrom et al (1973) has a spatial response function which can be represented by an isosceles triangle with a 30 μm FWHM as shown in Fig 5c The result of scanning the distribution of Fig 5b with this detector is displayed by the solid line in Fig 5d For comparison the dashed line in Fig 5d is Lindstrom et al s (1973) experimental result As in the example of Fig 4 the calculated trace is an additive composite of the responses to the separate triangular and rectangular distributions in Fig 5b (cf Figs 3a–c) The calculated and experimental trace in Fig 5d are similar in that 1) the width of the epithelial region is some 70 % that of the stromal region 2) the intensity at the epithelial peak is approximately twice the average stromal intensity and 3) the intensity at the endothelial peak is approximately 1 4

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[*]) This band is most likely scattering from the region of disorganized connective tissue in the anterior stroma This region includes Bowmans layer and the anterior most lamellae in which the fibrils turn up to merge with Bowmans The disorganized nature of the fibril arrangements in these areas is expected to increase the scattering power per fibril relative to the rest of the stromal fibrils

times the average stromal intensity This ageement between theory and experiment demonstrates that the experimental trace is consistent with some 72 % of the scattering originating from within the stroma which is the principal result of the present study

Although of secondary importance certain detailed features of the traces deserve mentioning First the experimental results show an apparent decrease of scatter intensity from the deeper layers of the stroma. This effect could be a consequence of structural variations with depth into the cornea however attenuation of the incident and scattered beams must be taken into proper account in the analysis before firm conclusions can be drawn Next the apparent (10–15) μm displacement of the experimental trace to the left of the calculated trace in Fig 6d is due in part to the fact that the ideal triangular response function used in the analysis does not include the tails of the measured response function Finally in the experimental geometry employed by Lindstrom et al (1973) one would expect the scattering to vary from one lamella to the next both because the angle between the incident beam and the fibril axis changes and because they used polarized light However it is not surprising that they did not observe this effect since their apparatus has an effective resolution of ~ 50 microns at the scattering angle they employed so that they were averaging over many orientation angles at each position

Summary and Conclusions

The present analysis demonstrates that most (~ 3/4) of the corneal scattering at 135° is from within the stroma The study of McCally & Farrell (1976) shows that a similar result holds at a variety of angles between 20° and 145° We are presently developing an instrument with better resolution which will permit depth dependent measurements at smaller scattering angles Such measurements are useful since most of the scattering is at these angles

Acknowledgments

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BACTERIAL FLORA IN RELATION TO CATARACT EXTRACTION

IV Postoperative inflammation The role of conjunctival bacteria and certain surgical factors

BY

J A FAHMY* S MØLLER** and
M WEIS BENTZON *

In 499 patients operated on for cataract the clinical postoperative signs of extraocular inflammation (conjunctival hyperaemia, chemosis discharge and oedema of the lids) the number of infiltrates around the corneo scleral sutures and the severity of intraocular inflammation in the anterior chamber (aqueous flare) were assessed on the fourth postoperative day and correlated with the bacterial conjunctival flora examined both qualitatively and quantitatively on the same day Patients with potential pathogens (*Staphylococcus aureus* gram negative bacilli and streptococci) on the conjunctiva following operation did not show any increased inflammatory reactions when compared with those without such pathogens The quantity of bacteria, i e. number of colonies did not appear to play a role The reasons are discussed

The clinical postoperative inflammatoy signs were further correlated with the following factors urgical complications quality of suturing technique use of alpha chymotrypsin systemic disea e sex and age A positive correlation was found bet een the severity of extraocular inflammation and

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retained lens material and hyphaema Furthermore extraocular reactions were more severe in males than females The incidence of infiltrates around corneoscleral sutures was found to vary with age i e occurred more frequently in patients < 60 years No relationship was found between the severity of aqueous flare and the above mentioned factors

Key words cataract extraction – bacteria – flora – postoperative inflammation – vital staining – corneoscleral sutures

In the immediate period following cataract extraction the eye normally reacts by showing a varying degree of extra as well as intraocular inflammation mainly as a result of the surgical trauma

This paper examines the relationship between the conjunctival bacteria isolated postoperatively and such inflammatory reactions The bacterial flora was studied on the fourth postoperative day and the results were correlated with the clinical findings assessed on the same day before the administration of any antibiotics or corticosteroids At the same time the influence of various other factors such as surgical complications suturing technique use of alpha chymotrypsin systemic disease sex and age on the occurrence and severity of post surgical inflammations has been examined

Material and Methods

The material is described in detail elsewhere (Fahmy et al 1975b) and comprises 499 patients admitted for senile or presenile uncomplicated cataract extraction to the Department of Ophthalmology Kommunehospitalet Copenhagen during the period 17 8 1972–16 5 1973

The methods of obtaining bacterial cultures preparation for surgery surgical technique and postoperative care have been described in previous papers (Fahmy et al 1975b c d)

Clinical methods All the patients were examined by one of the authors (J A F) on the fourth postoperative day before any antibiotics or steroids had been applied After the clinical findings had been assessed bacterial cultures were taken from the lower fornix and the tarsal conjunctiva This was followed by vital staining of the conjunctiva with tetrazolium alcian blue mixture (Norn 1971 1972 1974)

Statistical methods The relationship between the following clinical signs extraocular inflammation infiltrates around the corneoscleral sutures severity of reactions in the anterior chamber (aqueous flare) and the factors shown in Tables I III and IV as well as the interrelationship between these signs have been tested by χ test If the

expected numbers for any combination of groups or factors were found to be less than five some of the groups or factors were pooled before the test was carried out. The significance test mentioned in the text and used in Table II is also χ test applied to the comparison between two relative frequencies For all χ^2 tests the probabilities have been calculated by means of a computer programme In the study of the relation between the number of colonies of bacteria and the above mentioned clinical signs the following screening procedure has been used the correlation coefficients were calculated for each combination of bacteria and clinical sign treating the latter as a semiquantitave variable using only cases in which at least one colony of the bacteria in question was found If the correlation coefficient obtained in this way was significantly different from zero a χ^2 test was performed

Results

Postoperative extraocular inflammation

The material was divided into 3 groups according to the sum of the *relative severity* of the following clinical inflammatory signs hyperaemia of the con junctiva (mainly fornix close regions) chemosis oedema of the eye lids and finally type and amount of conjunctival discharge Group I included those patients showing *mild* inflammatory signs Group II *moderate* while Group III included patients with *relatively severe* inflammatory signs

Out of the total of 499 patients 473 were operated on with *silk sutures* (8–0) 18 with *collagen sutures* (6–0) while the suture material used with a further 8 patients was not recorded Of the group operated on with *silk sutures* 3 patients developed *endophthalmitis* (Fahmy 1975) *while 7 patients were not examined* by the author Of the remaining 463 patients 31 % showed relatively severe inflammation as opposed to 61 % out of 18 operated on with *collagen sutures* The difference is significant ($P = 0.0095$) Only cases operated on with *silk* were the subject of further analysis in the present study

Table I shows the number of patients as well as the incidence of *bacteria* (*Staphylococcus albus* corynebacteria, *Staphylococcus aureus* streptococci and *gram negative bacilli*) and sterile cultures By means of χ test no statistical difference could be found between the incidences of each microorganism in the different groups The same applied to the number of colonies of each micro organism when correlated with the grade of inflammation (see statistical methods)

The incidences of the *surgical complications* retained lens material prolapse or unintended lesion of the iris loss of the vitreous and hyphaema were exam ined and a positive correlation was found between the severity of extraocular inflammation and retained lens material ($P = 0.0030$) and hyphaema ($P = 0.0081$)

Table I

Correlation between the severity of extraocular inflammation and the examined factors

Factors	Postoperative extraocular inflammation				
	Mild (241 pts)	Moderate (79 pts)	Severe (143 pts)	Total (463 pts)	χ^2 test
Bacterial flora					
S albus	232	75	135	442	n s
Corynebacteria	23	3	6	32	n s
S aureus	17	3	10	34	n s
Streptococci	3	0	2	5	n s
Gram negative bacilli	8	3	5	16	n s
Sterile cultures	5	3	2	10	n s
Surgical complications					
Retained lens material	9	7	19	35	$P = 0.0030$
Prolapse/lesion of iris	22	6	12	40	n s
Loss of vitreous	10	7	14	31	n s
Hyphaema	18	12	25	55	$P = 0.0051$
Other surgical factors					
Inadequate conjunctival suturing technique	24	5	17	46	n s
Inadequate corneoscleral suturing technique	16	4	10	30	n s
Alpha chymotrypsin	20	8	11	39	n s
Systemic disease					
Arterial hypertension	20	8	16	44	n s
Diabetes mellitus	20	7	7	34	n s
Pulmonary disorders	5	3	8	16	n s
Cardiac disorders	31	7	14	52	n s
Age					
< 60	25	10	14	49	n. s
60–69	57	20	35	112	
70–79	100	28	66	194	
≥ 80	59	21	23	103	
Sex					
Males	81	31	69	181	$P = 0.045$
Females	160	48	74	282	

Figures in brackets indicate the number of patients n s = *not significant*

Table II

Correlation between the severity of extraocular inflammation and the results of vital staining of the conjunctiva with tetrazolium alcian blue mixture.

Vital staining with tetrazolium alcian blue mixture (Norn 1972)	Postoperative extraocular inflammation			
	Mild	Moderate	Severe	Total
Predominantly blue *	202	63	109	374
Predominantly red **	32	13	31	76
Not examined *	7	3	3	13
Total	241	79	143	463

* The amount of *mucus* (around conjunctival sutures corneoscleral sutures and in the lower mucus thread) is greater than the amount of *pus*

** The amount of *pus* (around conjunctival sutures corneoscleral sutures and in the lower mucus thread) is equal or greater than the amount of *mucus*

** Including 6 patients with indefinite colour

The incidences of the *surgical factors* inadequate conjunctival and corneo scleral suturing technique use of alpha chymotrypsin as well as the incidence of *systemic disease* (arterial hypertension diabetes mellitus pulmonary and cardiac disorders) and *age* did not vary significantly among the inflammatory groups There was a sex difference, and relatively severe inflammation occurred significantly more frequently among males than females ($P = 0\ 045$)

Table II relates the results of staining the conjunctiva with tetrazolium alcian blue mixture to the grade of inflammation No significant correlation could be found between the results of staining the conjunctiva and grade of inflammation

Infiltrates around corneoscleral sutures

Of 473 patients operated on with silk sutures 63 patients (13 3 %) were not or could not be examined as the sutures were not visible under the conjunctiva

Table III shows the number of patients and correlates the number of infil trates with the incidence of bacteria No significant relationship could be found The same applied to the number of colonies of each microorganism when correlated with the number of infiltrates (see statistical methods) The other factors examined in Table I were correlated with the number of infiltrates Only *age* seemed to play a role patients ≤ 60 years showed the highest incidence

Table III

Correlation between the number of infiltrates around corneoscleral sutures and the incidence of bacteria

Bacteria	Number of infiltrates around corneoscleral sutures					
	None (318 pts)	1 (53 pts)	2 (22 pts)	≥ 3 (17 pts)	Total (410 pts)	χ test
S albus	306	50	20	15	391	n s
Corynebacteria	20	2	1	3	26	n s
S aureus	23	3	2	3	31	n s
Streptococci	3				3	n. s
Gram negative bacilli	10	2	4		16	n. s
Sterile cultures	7	2	1		10	n s

n s not significant

Table IV

Correlation between the severity of aqueous flare in the anterior chamber and the incidence of bacteria

Bacteria	Postoperative intraocular inflammation (aqueous flare)					
	None (155 pts)	Mild (127 pts)	Moderate (56 pts)	Severe (39 pts)	Total (377 pts)	χ test
S albus	150	124	54	36	364	n s
Corynebacteria	8	10	3	1	22	n s
S aureus	16	7	3	1	27	n s
Streptococci	2	1			3	n s
Gram negative bacilli	7	3	4	3	17	n s
Sterile cultures	2	1	1	2	6	n s

n s not significant

while those ≧ 80 years had the lowest incidence of infiltrates ($P = 0.0030$) However it must be born in mind that this significance could be chance significance since many calculations were performed in the present study

Postoperative intraocular inflammation (aqueous-flare)

The postoperative reactions in the anterior chamber were graded into four groups according to the severity of *aqueous flare* Grade 0 signified no pathological flare grade 1 mild grade 2 moderate while grade 3 represented cases with relatively severe flare

Of 473 patients operated on with silk 96 (20 3 %) patients were not or could not be examined because of coincidental hyphaema or oedema of the cornea

Table IV shows the number of patients and the incidence of bacteria in each of the four groups No significant relationship could be found The number of colonies of each microorganism (see statistical methods) and the above mentioned factors in Table I (except hyphaema) have also been correlated with the severity of aqueous flare and no relationship could be found

The three clinical signs extraocular inflammation number of infiltrates and severity of aqueous flare in the anterior chamber have been treated separately in the above analysis χ tests have shown that those signs were not independent A positive correlation was found between the severity of extraocular inflammation and severity of aqueous flare in the anterior chamber ($P < 0.0005$) and between the number of infiltrates and the severity of aqueous flare in the anterior chamber ($P < 0.025$) Therefore it was investigated whether the conclusion of the separate analysis was changed when combinations of the three clinical signs were considered The whole material was divided into two groups for each sign giving a total of eight combinations The same significances were found Furthermore in patients showing the severest signs of extraocular inflammation a significant relationship was found between the factors inadequate conjunctival and corneoscleral suturing technique and the presence of infiltrates around the corneoscleral sutures ($P < 0.05$ and < 0.01 respectively)

Discussion

The main object of the present study was to examine the role of conjunctival bacteria isolated postoperatively in the enhancement of extraocular and intraocular inflammation following cataract extraction

It has been stated (Gradle 1910 Lowenstein 1911 Liebermann & Lengyel 1911 Berens & Bogart 1938 Hughes & Owens 1947 Hogan 1957 Aronson &

Elliott 1972) that bacteria present on the conjunctiva per or postoperatively were one of the factors responsible for postsurgical uveitis In an experimental study undertaken on the corneas of guinea pigs McMaster et al (1970 1971) demonstrated that the postsurgical inflammatory reactions in animals delivered raised and operated on under germfree conditions were less severe than in those raised under normal conditions or infected with *S albus* They concluded that *S albus* can produce a severe inflammatory reaction in the anterior ocular segment if it is present per or postoperatively

In the present study which seems to be the only one of its kind in the literature no relationship could be found between the severity of the clinical postoperative signs and types and number of conjunctival bacteria This seems to be remarkable especially the fact that patients carrying potential pathogens (*S aureus* gram negative bacilli and streptococci) on their conjunctivas showed no more postsurgical inflammatory reactions when compared with those without such pathogens A similar phenomenum was observed elsewhere (Fahmy et al 1975b) when the types and number of bacteria isolated from normal conjunctivas were correlated with the number of polymorphonuclear neutrophils recovered from the conjunctival fluid and again no relationship could be found It was postulated (Fahmy et al 1975b) that the antibiotic properties of the normal ocular flora (Halbert 1972) the action of lysozyme and the content of specific antibodies in the tears were probable factors counteracting the potential danger of those pathogens and preventing neutrophilic reactions The same could be said of the results in the present study The above mentioned protective factors might have neutralized the action of pathogens and prevented the enhancement of postsurgical inflammatory reactions

The relationship of postoperative infections (including the three cases with endophthalmitis observed in the present study) to the bacterial flora has been discussed elsewhere (Fahmy 1975)

Apart from the above mentioned microbial factor it is likewise stated (Berens & Bogart 1938 Hughes & Owens 1947 Theodore 1964 Records 1967 Aronson & Elliot 1972) that genetic constitution presence of systemic disease duration of procedure type and diameter of suture material extent of intraocular manipulations surgical complications and unsuspected retained intraocular foreign body introduced at the time of surgery were factors responsible for the enhancement of postsurgical inflammatory reactions

Of the factors examined in the present study retained lens material hyphaema sex and age seemed to play a role Furthermore in patients showing the relatively severest signs of extraocular inflammations the quality of suturing

technique seemed to influence the incidence of infiltrates around the corneo scleral sutures The nature of those infiltrates has been studied by Norn (1972a) and was found to be due to myriads of neutrophilic leucocytes Aronson & Elliott (1972) claimed that those infiltrates were caused by indigenous bacteria such as *S albus* corynebacteria and streptococci However the present study could not confirm this supposition It seems most likely that the infiltrates are due to a toxic reaction caused by the silk sutures

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OPTICAL ASPECTS OF THE MEASUREMENT OF DIFFERENCES IN ELEVATION OR DEPRESSION IN THE FUNDUS OCULI

BY

ULF HALLDÉN

The relation between differences in elevation of the fundus oculi and differences in refraction is influenced by the length of the optical axis of the eye This influence is important when measurements are performed by accurate modern methods

Key words refraction – optic disc – optical axis (length of) – fundus oculi (elevation of)

When the protrusion of the optic disc is measured by direct ophthalmoscopy it is an old and well established dictum that three diopters difference of refraction corresponds to one mm of elevation This rule is approximate but the method of measurement is not very exact.

However at the present time after the introduction of much improved methods of measurement (Krakau et al 1972) it seems useful to discuss how the optical properties of the eye under investigation might influence such measurements

The simplest way is to begin with Gullstrands wellknown equation $B = A + D$ If n is the index of refraction of the aqueous and the vitreous b the length of the optical axis of the eye Δb the elevation in the fundus oculi L the difference

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of refraction A the refraction of the eye and D the dioptric power of the optical system of the eye the distances measured in m the vergences in diopters the following equations are found

$$\left.\begin{aligned} \frac{n}{b} &= A + D \qquad (1) \\ \frac{n}{b - \Delta b} &= (A + L) + D \qquad (2) \end{aligned}\right\}$$

A and D are eliminated by subtraction

$$\Delta b = \frac{Lb^2}{n}\left(1 - \frac{\Delta b}{b}\right) \qquad (3)$$

$$L = \Delta b \frac{n}{b} \quad \frac{1}{1 - \frac{\Delta b}{b}} \qquad (4)$$

If L exceeds 5 D and if an exact result is desired it will be necessary to take into account the distance between the point of measurement and the anterior principal point of the eye If L^1 is the difference of refraction measured at a point g m from the anterior principal point, an exact result is found if the following expression is substituted for L

$$\frac{L^1}{1 - gL^1} \qquad (5)$$

The resulting complexity of the equations is apparent rather than real the solution can be achieved in a few minutes with a simple pocket calculator

To facilitate a presentation in diagrams an approximation of eq 3 and 4 is performed If Δb is small the expression $1 - \frac{\Delta b}{b}$ differs little from unity This will give the approximate equations

$$\Delta b \approx \frac{Lb^2}{n} \qquad (6)$$

$$L \approx \Delta b \frac{n}{b^2} \qquad (7)$$

valid only when Δb and L are small The error caused by this will very seldom exceed 10 % if $\Delta b \leq 2$ mm and $L \leq 5$ D

Equations 6 and 7 are illustrated in the diagrams (Figs 1 and 2) For n the value 1 336 is used It is seen that variations of b will greatly influence the relation between L and Δb In an axially hypermetropic eye of +9 an elevation

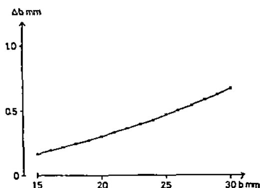


Fig 1
The height of elevation which causes a difference in refraction of 1 D at different values of the length of the optic axis of the eye.

of 1 mm corresponds to a difference of refraction of more than 3.5 D in the simplified schematic eye of Gullstrand to 2.5 D and in an axially myopic eye of –15 to 1 5 D

This source of error can be very disturbing when measurements are made by accurate methods by a range finder mounted on a Gullstrand ophthal moscope (Krakau 1949) by stereo photographs (Krakau 1956) or by slit image

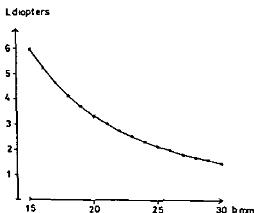


Fig 2
The difference in refraction caused by an elevation of 1 mm at different values of the length of the optic axis of the eye.

photogrammetry (Holm & Krakau 1970) Even if a Goldmann contact glass (-64 5 D) is used to eliminate the dioptric power of the eye the importance of b remains unchanged If accuracy is desired it is necessary to measure the length of the axis of the eye. This can easily and with sufficient precision be done with ultrasound The more accurate method of Rushton (Stenstrom 1946) is unnecessarily laborious

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CENTRAL CORNEAL THICKNESS IN NEWBORNS AND CHILDREN

BY

NIELS EHLERS TORBEN SØRENSEN
THORKILD BRAMSEN and ERIK HOLK POULSEN

Central corneal thickness was measured optically in premature and full term babies and in children The thickness was found to decrease from the values found in premature and full term babies to those found in small children aged between 2-4 years The thickness of the adult cornea is reached at the age of about 3 years
These findings are discussed with respect to the possible role of corneal thickness as a biometric parameter to intraocular pressure measurement and to corneal thickness steady state regulation.

Key words biometry – corneal thickness – premature – newborn – children – intraocular pressure – hydration

No age variation in central corneal thickness has been found in adults (von Bahr 1948 Lavergne & Kelecom 1962 Martolo & Baum 1968 Lowe 1969 Kruse Hansen 1971) This apparent stability of the thickness seems very interesting as the thickness may prove to be an individual specific measure a biometric parameter From this point of view the correlation of corneal thickness to other ocular dimensions was studied and it was found to be a relatively independent dimension (Ehlers Kruse Hansen & Aasved 1975) The apparent stability of

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the thickness is interesting when hydration and transparency control are considered as it suggests the existence of regulatory mechanisms

Central corneal thickness is an important parameter in the determination of the intraocular pressure by applanation tonometry (Ehlers Bramsen & Sperling 1975) Consequently knowledge of corneal thickness in the small child would appear to be important in the diagnosis and control of buphthalmia

In the literature no data on central corneal thickness in children could be found It was therefore decided to study this aspect and to include premature and full term children A change in thickness after birth might represent a further argument for the existence of regulating factors

Material and Methods

The study comprised 61 children There were 6 premature babies and 19 full term babies born at *Fodselsanstalten in Jylland* In these two groups corneal thickness and curvature of the mothers were also measured Ten children aged from 2–4 years 15 aged from 5–9 years and 11 aged from 10–14 years were also examined These were mainly children of the hospital staff all with a normal eye examination and refractions within ± 2 D

Central corneal thickness was measured optically with the Haag Streit pachometer modified according to Mishima & Hedbys (1968) as previously described (Ehlers 1974) Horizontal corneal curvature was measured with a Haag Streit keratometer and thickness readings corrected according to this using the correction table supplied by Haag Streit The small children were held in front of the slit lamp and the keratometer by assistants

Evaluation of the data was made according to the directions of Sokal & Rohlf (1969) Values are given as mean ± standard error of mean and significance tested by the *t* test Adult corneal thickness shows a frequency distribution which does not differ from the normal curve

Results

Central corneal thickness The obtained data are shown in the Table I The average thickness in the group of premature babies was 0 545 ± 0 014 mm while in the group of full term babies it was 0 511 ± 0 006 mm The difference between these two groups is not statistically significant The three groups of children aged 2–4 5–9 and 10–14 years respectively all showed an average thickness of 0.520 mm The thickness in the group of full term babies is significantly higher than in any of the other three groups of children ($P < 0.025$ 0 01 and 0 025 respectively)

Table I

Central corneal thickness and curvature in newborns and children

Group	No	CCT mm ± SEM	R mm ± SEM
Premature newborns	6	0 545 ± 0 014	6 35 ± 0 09
Mature newborns	10	0.541 ± 0 006	7 11 ± 0 07
Children 2–4 years	10	0 520 ± 0 007	7 73 ± 0 09
Children 5–9 years	15	0.520 ± 0 005	7 81 ± 0 09
Children 10–14 years	11	0.520 ± 0 007	8 01 ± 0 05
Adults own groups and data from literature		~ 0.52	~ 7 8

The data apply to right eyes Essentially similar values were found for left eyes

Corneal curvature The data appear from Table I As expected the smaller eyes of the premature and full term babies have a more curved cornea Adult values are reached at about 3 years of age

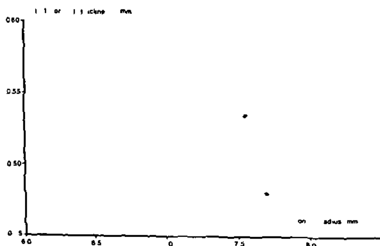


Fig 1

Correlation between horizontal corneal radius and central corneal thickness in mm There is a tendency towards decreasing thickness with increasing radius ($r = -0.4$, $P < 0.01$)

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THE TREATMENT OF GLAUCOMA WITH PROPRANOLOL (INDERAL®) A CLINICAL TRIAL

BY

ANDERS BORTHNE

The effect of propranolol (Inderal®) on the intraocular pressure (IOP) in glaucoma has been measured Twenty two patients completed the clinical trial Propranolol in doses of 160 mg/d effectively lowered IOP in eyes with various types of open angle glaucoma. The test periods lasted from 4 to 6 days The ocular hypotensive effect of propranolol was also registered in patients efficiently treated with pilocarpine and acetazolamide (Diamox®) and in glaucomas not satisfactorily controlled by this therapy High positive correlations between mean pretreatment pressure (P_1) and pressure fall (ΔP) were found ($P < 0.001$) and the pressure decrease induced by propranolol treatment tended to be proportional to the pressure gradient between the anterior chamber and the episcleral veins This pressure gradient was reduced by an average of about 50% following propranolol treatment. There was no change in scleral rigidity after propranolol

Key words propranolol – Inderal® – glaucoma – beta adrenergic blockers

The beta adrenergic blocking agent propranolol has been reported to reduce the intraocular pressure (IOP) following both systemic and topical administration (Phillips et al 1967 Cote & Drance 1968 Bucci et al 1968 Vale & Phillips

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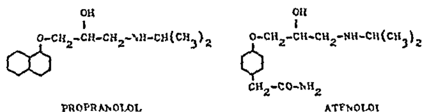


Fig 1
Chemical structure of the beta adrenergic blocking drugs propranolol (Inderal®) and atenolol (Tenormin®)

1970 Musini et al 1971 Bietti 1972 Tieri & Pozella 1975) Other studies suggest that other beta blocking drugs are similarly effective (Bonomi & Steindler 1975 Elliot et al 1975)

The exact mode of action of these compounds is unknown Propranolol blocks both $beta_1$ receptors which transfer excitatory sympathetic impulses (cardiac contractility) and $beta_2$ receptors which transfer inhibitory impulses (bronchodilatation) Whether one or both of these receptors exist in the human eye is speculative (Vale & Phillips 1973) The membrane stabilizing activity of propranolol and the mild beta mimetic action demonstrable before beta inhibition may also account for the reduction of IOP It is however doubtful if these pharmacological properties have any clinical relevance since atenolol which is devoid of these side effects also seems to lower IOP in human eyes (Elliot et al 1975)

While propranolol eye drops have a local anaesthetic effect which precludes its clinical use oral propranolol has been found useful in the treatment of glaucoma patients (Ohrstrom 1973 Pandolfi & Ohrstrom 1974)

The aim of this investigation was to further elucidate the effect of propranolol on IOP in open angle glaucoma

Material and Methods

The trial was started as a double blind cross over trial of propranolol and placebo and was completed as such except that during the trial several patients complained to the examiner of a slow pulse rate This together with a very marked change in pressure level at the beginning of either the first or the second period of treatment in fact revealed the identity of the drug in use. The trial is therefore classified as a clinical trial

Table I
Diagnostic classification of eyes in the trial

Diagnosis	Number of eyes		
	Normal visual field	Visual field defect	Total
Simple glaucoma	20	4	24
Capsular glaucoma	5	5	10
Suspected glaucoma	2		2

The parameter measured was the intraocular pressure Observations were made on 22 patients who were selected from the Eye Clinic and who were hospitalized during the trial There were 13 men and 9 women ranging from 49 to 84 years of age and averaging 63 5 years

In 6 cases of the original test group sclerostomy had been performed in one eye These 6 eyes were later excluded from the material

Table I shows the diagnostic classification of eyes included in this material Twenty five eyes had constant or intermittent IOP greater than 24 mmHg but no visual field or optic nerve abnormalities Nine eyes had pathologically raised IOP with visual field defects and optic disc cupping typical of glaucoma. The 2 eyes classified as suspected glaucoma had intermittently IOP of 21 mmHg The fellow eyes were glaucomatous in both cases

The patients are divided into three groups according to treatment given (Table II) *Group A consists of patients who had* propranolol and placebo as the only treatment Group B comprises 8 cases treated with pilocarpine eye drops and group C 6 patients who *received topical pilocarpine plus oral Dia* mox® Pilocarpine and Diamox® had been used by the patients for a variable length of time before the trial (a few days to several years) and was continued without any pause at the same dosage for each individual during the trial 2 % pilocarpine eye drops 3–5 times daily and Diamox® in the sustets form 500 mg/day were administered by a nurse to each patient

The details of the trial were explained to each patient, and consent was obtained Each *individual was assigned to* either propranolol or placebo as determined by a table of random numbers

The doses of propranolol were standardized at 160 mg/day and were given in individual doses of 40 mg at 7 15 11 a m 3 00 and 7 00 p m supervised by a nurse

Table II
Mean change in intraocular pressure after propranolol

Group	Case No	Age (years) Sex	No of days tested	Mean pretreatment pressure RE	LE	Mean pressure fall RE	LE
	1	68 M	5	35 2 ± 3 2	34 9 ± 3 1	11 2 ± 2 [illegible]	10 [illegible] ± [illegible] 7
	2	56 F	4		36 5 ± 3 6		1[illegible] [illegible] ± 3 2
	3	67 F	5	21 7 ± 4 2	27 2 ± 3 9	6 9 ± 4 0	[illegible]4 ± 3 4
A	4	68 M	4	25 2 ± 2 5	24 9 ± 2 2	5 0 ± 2 8	5 3 ± [illegible]2
	5	69 M	5	21 5 ± 2 4	22 6 ± 2 0	[illegible]0 ± 2 8	[illegible]3 ± [illegible]
	6	60 F	6	17 7 ± 1 9	2[illegible] 8 ± 2 1	3 6 ± 0 9	5[illegible] ± 1 6
	7	68 F	5		21 1 ± 2 0		[illegible] ± [illegible]5
	8	69 F	6	19 5 ± 2 1	16 4 ± 2 4	6 0 ± 1 [illegible]	3 [illegible] ± [illegible]
	9	64 M	6	2[illegible] 0 ± 5 2	21 1 ± 1 7	9 0 ± 3 8	5 1 ± 1 4
	10	[illegible]0 F	6		21 8 ± 2 4		6 7 ± 2 2
	11	51 M	6	3[illegible] [illegible] ± 3 4	19 3 ± 2 7	17 5 ± 3 9	7 [illegible] ± 3 4
B	12	49 F	4	18 4 ± 3 6		3 3 ± 3 2	
	13	56 M	4	20 9 ± 2 4	20 1 ± 1 9	5 9 ± 2 3	4 5 ± [illegible]4
	14	59 M	4	18 3 ± 4 8	24 8 ± 6 3	3 3 ± 3 0	6 9 ± 4 [illegible]
	15	84 M	5	24 9 ± 8 8		7 5 ± 5 3	
	16	63 F	6	18 7 ± 1 7	20 9 ± 2 8	3 6 ± 1 [illegible]	4 8 ± 1 6
	17	49 M	5	25 6 ± 4 5	18 9 ± 2 5	14 2 ± 4 0	6 2 ± [illegible]6
	18	[illegible]2 M	6		30 3 ± 4 5		7 4 ± 4 7
C	19	71 F	6	22 2 ± 4 1	25 3 ± 4 8	6 2 ± 3 4	6 9 ± 4 9
	20	63 M	6	24 6 ± 2 7	18 3 ± 2 2	8 2 ± 2 5	4 ± 1 5
	21	59 M	4	14 6 ± 1 7	13 9 ± 2 3	2 5 ± 1 5	[illegible]8 ± 1 7
	22	61 M	4		22 1 ± 2 9		4[illegible] ± 3 9

All figures are mean ± 1 standard deviation
Additional treatment A none B 2 % pilocarpine eye drops 3–5 times daily
C 2 % pilocarpine eye drops 3–5 times daily plus oral Diamox® 500 mg daily

The tablets of propranolol and placebo were provided by I C I Pharmaceutical Company The key to the randomization codes was kept by the local pharmacist and was unknown to the examiner until the trial was completed Eleven patients started with propranolol and 11 patients started with placebo

Each patient had an ECG and a chest X ray taken and these were studied by the department of internal medicine before the trial was started

The intraocular pressure was measured by the author at 8 15 a m and at 5 30 p m each day using a Haag Streit applanation tonometer

Each treatment period lasted from 4 to 6 days The placebo and the propra nolol periods were of the same length for each patient The measurement taken on the morning of the first day of the second period of *treatment* was *ignored* in order to avoid carry over effects and an extra measurement was made at the end of that period for inclusion in the analysis

The following standard statistical methods were used Student s *t* test the least squares method and standard deviation = $\sqrt{\frac{\Sigma (x - \bar{x})}{n - 1}}$

Results

The tonometric data were evaluated in two ways Firstly the arithmetic means of all pressures which were measured in each eye during each treatment were calculated These figures (Table II) comprise the average of 8 to 12 measure ments Without further statistical analysis it is evident that in all cases the mean pressures measured with propranolol were consistently lower than those

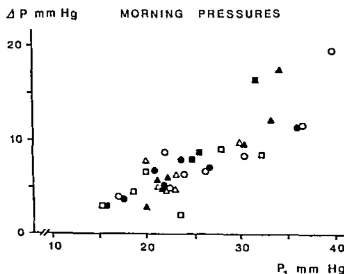


Fig 9

Mean morn ng pressures measured with placebo (P_1) are plotted against mean decrease in IOP following propranolol treatment (ΔP) Black marks represent right eyes and white marks left eyes Symbols group A = ○ group B = △ group C = □ Correlati n coefficients 0 785 ($P < 0.001$) for right eyes and 0 03 ($P < 0.001$) for left eyes

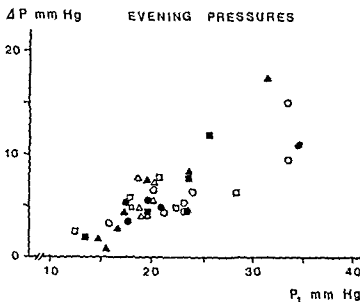


Fig 3

Mean evening pressures *Ordinate* mean decrease in IOP following propranolol treatment (ΔP) *Abscissa* mean pretreatment pressure (P_1) Correlation coefficients 0 [illegible]5 ($P < 0.001$) for right eyes (black) and 0 [illegible]87 ($P < 0.001$) for left eyes (white)

measured with placebo The difference between mean placebo pressure and mean propranolol pressure was therefore indicated in Table II as mean pressure fall

Table II shows that the decrease of IOP induced by propranolol treatment ranged from 2 5 mmHg (Case 21 R) to 17 5 mmHg (Case 11 R) on average

In another method of evaluation the mean morning and mean evening pressures for each eye were compared before and after propranolol This is pertinent owing to the diurnal pressure variations A plot was made for the placebo pressure (P_1) versus the fall in pressure (ΔP) after treatment *with propranolol* This relationship is illustrated separately for morning and evening pressures in Figs 2 and 3 The effect of propranolol is very clear in both graphs *In* all cases IOP is lower with propranolol than with placebo and this applies to both eyes morning and evening The figures also illustrate that there is an approximately linear relationship between P_1 and ΔP

The results of the regression analysis are shown in Table III The correlations between the pressure fall after propranolol and the pretreatment pressure are statistically highly significant ($P < 0.001$) Right and left eyes are separately analysed owing to the varied correlations between paired eyes

Table III

Correlations for pretreatment pressure (P_1) and pressure fall after propranolol (ΔP)

Material	No of eyes	Intercept on P_1 axis a	k	t	Correlation coefficient r
Morning					
ABC Right eye	17	19.5	0.63	4.91	0.785 ($P < 0.001$)
ABC Left eye	20	10.5	0.50	4.19	0.[illegible]03 ($P < 0.001$)
Evening					
ABC Right eye	17	11.7	0.67	4.59	0.[illegible]75 ($P < 0.001$)
ABC Left eye	20	6.7	0.40	3.08	0.587 ($P < 0.001$)

$$t = r\sqrt{\frac{n-2}{1-r}}$$

Table IV shows the maximum daily pressure variations for each eye with placebo and propranolol. The figures are the results of two daily measurements and they are defined as the differences between morning and evening pressures for the same eye on the day of maximum pressure fluctuation.

Of the 37 eyes 30 had smaller maximum daily pressure fluctuations after propranolol. The same results were obtained from both right and left eyes, namely that there is a significant fall in the maximum daily pressure variations following the administration of propranolol ($P < 0.005$).

Table IV

Influence of propranolol on maximum daily ocular pressure variations

Material	No of eyes	Mean of max variations in P_1 ± 1 SD	Mean fall in max pressure variations ± 1 SD	P
ABC Right eye	17	7.[illegible] ± 4.2	3.4 ± 3.[illegible]	$0.001 < P < 0.005$
ABC Left eye	20	6.8 ± 3.1	1.6 ± 2.0	$0.001 < P < 0.005$

Scleral rigidity was measured by applanation tonometry and Schiotz tonometry with a 5.5 g plunger in 20 eyes of 10 patients and there was no significant change in the scleral rigidity coefficient after propranolol.

Side effects

Six patients were anxious about the slowing of their pulse rate. ECG control revealed sinus bradycardia. Two patients complained of nausea and one patient had insomnia and slight dizziness at the onset of the propranolol period. In all cases the medication was continued at the same dosage throughout the trials.

Discussion

The present trial has shown that propranolol in doses of 160 mg/d effectively lowered IOP in eyes with various types of open angle glaucoma. The marked pressure lowering effect of propranolol was also registered in chronic simple glaucomas with optic disc cupping and visual field defects. Eyes which had been treated for years with miotics (pilocarpine) and carbonic anhydrase inhibitor (Diamox®) and which during the trial were treated continuously with topical pilocarpine or pilocarpine plus Diamox® by mouth also responded well to propranolol treatment. Even the glaucomas which were not satisfactorily controlled by pilocarpine and Diamox® showed a striking pressure fall after propranolol.

Figs. 2 and 3 show the correlation between mean IOP before treatment (P_1) and the pressure fall induced by propranolol (ΔP). This relationship approximates linearity in both graphs which means that the plotted values approximate to an equation

$$\Delta P = k (P_1 - a)$$

The values of k and a are found by regression analysis and the results are presented in Table III. The values of k and a are about the same in all groups, the average values being a = 10.3 mmHg and k = 0.55.

The value for P_1 intercept (a) is about the same as the episcleral venous pressure (p_v). This means that the pressure fall induced by propranolol treatment tends to be proportional to the pressure gradient between the anterior chamber and the episcleral veins.

Hydrodynamical calculations (Davanger 1965) show that this is to be expected when either the aqueous formation is reduced or the pore diameter in the outflow pathways is increased by a certain percentage or both. The per

centage effect of propranolol on these parameters is then probably about the same at all pressure levels

The value of k shows that the pressure gradient P_1 a = P_1 p_v is reduced by about 50 % on average by propranolol treatment (in group A 49 5 % in group B 48 % in group C 55 5 %)

The results achieved from this experiment thus make calculation of the approximate pressure fall (ΔP) possible when the initial pressure level (P_1) in a chronic simple (open angle) glaucoma is known presuming that 160 mg/d of propranolol is to be used

The magnitude of the maximum daily pressure variations (Table IV) de creased significantly after propranolol ($P < 0\ 005$)

Generally diurnal pressure variations decrease in a regular manner with falling pressure level (Davanger 1964b) This would ensue both a constant percentage inflow variation for different pressure levels (Grant 1955 Davanger 1964a) and a constant percentage variation in pore diameter in the outflow channels during the day (Davanger 1964a)

The observed changes in the maximum daily pressure variations in this material are probably due to the same hydrodynamic laws regardless of whether propranolol acts on the inflow or on the outflow systems of the eye or both The effect of propranolol is therefore primarily one of a lowering of the ocular pressure level alone The effects on the diurnal pressure variations are secondary

This trial has shown that propranolol is a powerful ocular hypotensive drug which is also effective when IOP is poorly controlled by pilocarpine eye drops and oral Diamox® Propranolol is now widely used with multiple indications in internal medicine and the possibility of masking the symptoms of glaucoma must be borne in mind Regardless of its many limitations propranolol seems to be a suitable drug for selected glaucoma patients When it is indicated for other reasons such as high blood pressure angina pectoris or cardial arrythmias it could probably be used as the sole means of therapy for glaucoma

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PRODUCTION OF HUMAN LENS CAPSULE ILLUSTRATED BY A CASE OF CHRONIC LENTICULAR CHALCOSIS

BY

JOHAN H SELAND

The osmiophilic capsular inclusion bodies in a case of accidental lenticular chalcosis have been used as an *in vivo* indicator of capsular production Copper stimulation and hence inclusion impregnation lasted 5 years and was stopped   years before removal of the lens by extraction of a foreign body The amount of capsule produced in the two year period varied at different locations in the lens but it greatly exceeded the previously measured quantities A capsular turnover is postulated with a capsular production by the epithelial cells and a surface resorption process The production rate is considered to be relatively high in childhood and gradually subsides with increasing age

Key words lens capsule – capsulogenesis – chalcosis – electron microscopy

The method commonly used when investigating the growth of the human lens capsule has been some form of thickness measurement in a series of lenses of various ages (Salzman 1912 Fisher & Pettet 1972) The annual increase in thickness does not equal the annual production of capsular material as thinning occurs due to increasing volume of the lens substance (Fisher & Pettet 1972 Nordmann et al 1974) In addition the total thickness will be modified by any resorption

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of capsular material from its surface The only way to determine the annual production of capsular substance by the epithelial cells would be to incorporate *a readily traceable marker in the capsule in vivo and measure its distance from* the cells at various time intervals

In experimental procedures incorporation of silver nitrate and of radioisotopes have been used to trace basement membrane production in animals (Kurtz & Feldman 1962 Young & Ocumpaugh 1966) Excessive copper stimulation also results in a readily traceable marker in the basement membranes of the eye Small osmiophilic inclusions appear probably as a result of a metabolic derangement caused by the toxic effect of copper on cellular enzymes (Awasthi et al 1975) The changes in the lens capsule result in the phenomenon referred to as sun flower cataract This entity was first described as a sequel to accidentally implanted copper (Purtcher 1918) Jess (1922) described the histological picture of lenticular chalcosis caused by copper implantation and found numerous small round inclusions in the anterior lens capsule forming a band or layer He also found copper in the superficial cortex of the posterior part of the lens The phenomenon may also appear in an inborn error of copper metabolism (Wilson s disease) or may be secondary to multiple myeloma (Ellis 1968 Lewis et al 1974) The ultrastructure of the deposited elements in Descemets membrane in Wilson s *disease were described and analysed by Uzman & Jakus (1957) The deposits* were histochemically shown to contain exchangeable copper This fact has been confirmed by energy dispersive X ray analyses (Harry & Tripathy 1970 Kanai et al 1974 Tso et al 1975) The ultrastructural changes of foreign body chalcosis was described by Hanna & Frauenfelder (1973) They demonstrated changes similar to those found in Wilson s disease but also more extensive confluent areas of osmiophilia and exfoliation of the capsule

Most of the reports in the present literature describing the effect of copper on the basement membranes of the eye have originate either from patients with a metabolic disease of uncertain duration or from patients with retained foreign bodies A case where a known copper stimulus has been present for an exact and known period of time will lend itself admirably to the study of capsular production

Material and Methods

A healthy male born in 1947 was subjected to a perforating eye injury caused by a cartridge explosion in January 1965 A brass fragment lodged near the optic nerve head in the right eye just in front of the retina without injuring the lens The vision was 6/6 on admission but later decreased to 6 24 due to retinal reaction The fragment was not removed as the operative risk was con

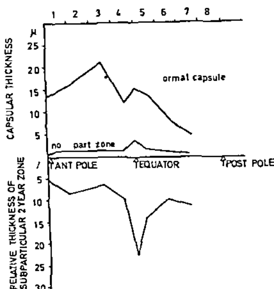


Fig 1

Curves showing the capsular thickness and thickness of subparticular zone (continuous lines) compared to normal thickness of unfixed capsule (dotted line – Fisher & Pettet 1972) The relative thickness of the subparticular zone is plotted as a percentage of the total capsule

sidered greater than the expected benefit. After the primary reaction had sub sided the eye became quiet 18 months after accident the first signs of sun flower cataract were noted 5 years after the original accident the metal frag ment presented itself at the anterior chamber angle and was removed surgically At operation the lens was seen to be subluxated and there was also an ordinary sclerosing cataract in addition to the chalcosis No Kayser Fleischer ring was ever observed

Following the operation the patient had periods of increased tension and several episodes of iridocyclitis which were effectively treated conservatively *with antiglaucoma drugs and steroids Exactly 2 years after the foreign body* had been excised (7 years after the original accident) an intracapsular lens ex traction was performed without using chymotrypsin The lens was immediately transfered to phosphate buffered glutaraldehyde and prepared for electron microscopy The lens was divided into 8 segments according to a previously described method (Seland 1974) and studied in a Phillips 300 EM electron microscope both after staining with uranyl and lead and when unstained Unfortunately the posterior pole was damaged during preparation

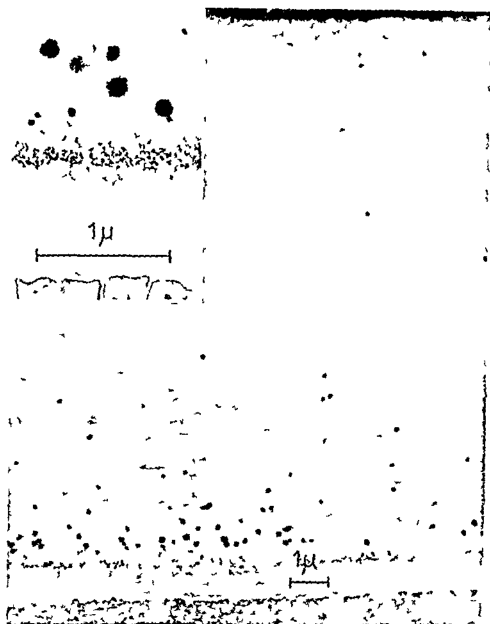


Fig 2

Section through the anterior capsule Area 2 4 000 Note the osmiophilic particles distributed throughout the capsular thickness apart from a zone adjacent to the epithelial cells Insert 16 000 section of the juxtacellular zone Note the size sequence of the particles



Fig 5

Anterior capsule area 4 × 16 000 Section from the equatorial subparticular zone Note the banded fibrils which seem to emerge from pits in the cellular surface The distance between the bands is about 520 Å



Fig 4
Posterior capsule × 3300 area 6 The inclusions are present but relatively few in number Note the distinct subparticular zone

Results

Changes were noted in all regions but they were particularly pronounced in the anterior capsule The thickness of the lens capsule in the various areas is tabulated in Fig 1 The thickness of the posterior capsule was within the normal range when shrinkage due to processing was taken into consideration However the central part of the anterior capsule was thicker than a normal average capsule In the anterior central area and in most sections of the *anterior capsule* numerous dense round dots were found near the cellular border (Fig 2) The particles lying deepest in the capsule were separated from the cell membranes by a layer of apparently normal particle free capsule of varying thickness In

the anterior capsule this layer was thickest near the equator where it measured up to 3 0 μ and thinnest in the central part where it measured 0 9 μ The particles in the anterior regions seemed to be arranged in a very distinct order the smallest sized dots measuring 80 Å were located nearest the cells the size increasing towards the capsular surface where they measured up to 2000 Å The particles were thus located in a zone with a well defined inner border and an illdefined superficial limit. In the central area numerous medium sized dots were found superficially were they almost reached the capsular surface (Fig 2) Some areas in the anterior capsule near the equator had very few dots and not such a distinct size sequence

In the pre equatorial region of the anterior capsule another striking feature was found namely bundles of banded (cross striated) fibrils emerging from pits at the cellular surface into the capsular substance The fibrils exhibited a periodicity of 520 Å (Fig 3) The direction of the fibril groups were both perpendicular and at angles to the cell membrane The surface of the anterior capsule showed an increased and irregular electron density

In the *posterior capsule* similar particles as the ones described above could be found but they were fewer than in the anterior capsule and no size sequence could be demonstrated A distinct layer of capsular substance free of particles was found adjacent to the lens fibres (Fig 4) This layer with low electron density was thinnest in the central area of the posterior capsule where it measured 0 6 μ gradually increasing towards the equator

Discussion

Numerous reports have described round osmiophilic electron dense dots in the ocular basement membrane as a result of copper influence caused by Wilson s disease multiple myeloma and accidentally implanted copper (Uzman & Jakus 1957 Johnson 1970 Tso Fine & Thorpe 1975 Ellis 1968 Lewis et al 1974 Hanna & Frauenfelder 1973) In this present case the zone or layer of particles must have been produced during the five year period when the epithelial cells were under the influence of copper Likewise the layer separating the particle zone from the cells represents the capsular material produced in the two year period following the removal of the foreign body until the extraction of the lens Fisher & Pettet (1972) have maintained that the maximal increase in capsular thickness occurs in the neonatal period with a 2–3 per cent annual growth The annual increase in thickness after puberty was considered by the same authors to be about 1 per cent per annum at the insertion of the anterior

Table I

RESORBTION OF SUNFLOWER CATARACT

AGE AT ACCIDENT	NO OF YRS REQUIRED FOR A COMPLETE (C) OR PARTIAL (P) RESORBTION	AUTHOR
2	10 (P)	JESS (1929)
5	10 (C) 4 YRS AFTER FOREIGN BODY EXTRACTION	JESS (1929)
6	8 (P)	CORDES & HARRINGTON (19..)
8½	6½ (C)	MULLER (1931)
10	8 (P)	MARNER (1945)
12½*	6 (C)	CAIRNS WILLIAMS WALSCHE (1969)
14	8 (C)	JESS (1929)
24	10 (C) 7 YRS AFTER FOREIGN BODY EXTRACTION	ZUR NEDDEN (1903)
25	6 (C)	JE S (1929)
28	14 (P)	JESS (1929)
32	10½ (C)	JESS (1929)
	10 (C)	ZAHOR (1930)

*START OF CHELATION TREATMENT FOR WILSONS DISEASE

zonular fibres This work has shown that the thickness of the particle free layer as a percentage of the total thickness constitutes a two year production varying from 5 to 23 per cent The layer at the insertion of the anterior zonular fibres was about 10 %

Assuming a constant capsular production rate half of these values would represent the annual increments The production of capsule in the central areas may be abnormally high as shown by an increased total thickness of the central part of the anterior capsule but the part of the capsule with a total thickness within the normal limits i e the peripheral part of the anterior capsule and the posterior capsule also show an annual production varying from 5 to 11 5 per cent An annual increase of capsular thickness of only one per cent as suggested by Fisher & Pettet (1972) cannot therefore be explained unless an active resorption of capsular material from the surface is assumed

One has to accept that the electron dense particles have been produced during the five year period of copper stimulation In some areas of the lens particularly near the anterior pole electron dense particles could be seen almost throughout the whole capsule (Fig 2) It seems however improbable that all this capsule could have been produced during the five year period unless copper itself is a powerful stimulus for capsular production and surface absorption Impregnation from without or some form of self propulsion may be part of the explana

tion The particles are probably lipoid complexes The presence of particles and a subparticular zone in the posterior capsule gives a strong indication that a continous renewal process exists even in this region The posterior capsulo neogenesis must originate from cells with a full complement of micro organelles i e the epithelial cells

The spontaneous disappearance of sun flower cataract reported in the literature may give another clue as to the rate of production of capsular material The time reported for such a disappearance to be complete varies from 4 to 10½ years and occurs mainly in young persons (Table I) It has been shown that any copper present in the inclusions has disappeared two years after removal of the foreign body (Seland 1976) The fading of the sun flower cataract is therefore probably not due to spontaneous or chelatic removal of copper but to the disappearance of capsular inclusion by capsulo neogenesis and absorption from the capsular surface

The production of capsular substance by the lens cells is probably much more active than hitherto generally accepted and the existence of a process resorbing capsular substance from the surface is highly probable. This work also shows that structures produced by epithelial cells may reach the capsular surface in a relatively short period of time

The production rates quoted here are not necessarily accurate for the normal lens but serve to illustrate that the epithelial lens cells under certain circumstances at least have the capability of responding to a stimulus with a high capsular production

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APPLANATION TONOMETRY IN THE CONSCIOUS CYNOMOLGUS MONKEY (MACACA FASCICULARIS)

BY

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Four monkeys (Macaca fascicularis) were trained to tolerate applanation tonometry while fully conscious The tonometer used was the Draeger tonometer with an applanation area of 3 06 mm diameter but with a reduced application surface (4 mm instead of 6 8 mm diameter) The re duction did not change the calibration and is applicable in this monkey species without any correction factor The mean intraocular pressure determined was 19 12 mmHg

Key words applanation tonometry – intraocular pressure – conscious monkey – Macaca fascicularis

Detailed examination of the monkey eye requires general anaesthesia Many of the data so collected remain unaffected by the anaesthesia but the intra ocular pressure (IOP) will be influenced by this In studies on the effect of drugs the influence on the IOP has apparently always been measured on un conscious monkeys the IOP in the untreated animal serving as the reference value If drugs are tested under general anaesthesia synergism or antagonism between drug and anaesthetic have to be considered Furthermore, an IOP

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lowering effect of any agent is difficult to demonstrate if the IOP is very low to start with as in barbiturate anaesthesia It is thus highly desirable that drug effects should either be measured in the conscious state or compared with the IOP in the conscious state The purpose of the present investigation was therefore to train monkeys to tolerate applanation tonometry while fully conscious and undrugged (apart from topical corneal anaesthesia) A slightly modified version of the tonometer originally described by Draeger (1966) was used

Materials and Methods

Animals Four young cynomolgi (Macaca fascicularis) weighing between 2 2 and 3 9 kg (3 males and 1 female) were used They were selected as being the tamest of about 2 dozen monkeys

Training The training was based on the idea of teaching the monkey by an award conditioned behaviour Apples which seemed to be the favourite fruit were used as the award They were not provided in the daily food ration but only after the animal had accomplished a given task The required task was made progressively more difficult At the start the monkey was simply conditioned to being removed from its cage This act was rewarded with an apple which was awaiting the monkey on its return to the cage At the completion of the training – after about 10–14 weeks – the monkey had to tolerate a complete tonometry in order to receive an apple The apples were placed in a transparent box on the top of the cage inaccessible but clearly visible to the monkey for about 20 min before the daily training



Fig 1
Holding a monkey between the thighs of an assistant The animal is slightly restrained without being stressed



Fig 2
Performance of tonometry with the reduced tip of a Draeger tonometer with 3 fingers on the skull of the monkey and the thumb pressed under the mandible the investigator lifts the right eyelid keeping the head of the animal in a firm grip

Every day at precisely 10 o clock (a m) the monkeys were removed from the cages by an assistant who covered his hands and forearms with thick leather gloves The investigator himself did not wear gloves and was in fact never bitten The animal was treated very gently but firmly We talked to them in a soft voice which was raised sharply if the animal became too agitated *Several positions were tested where the animal was restrained slightly* but which otherwise interfered with its comfort as little as possible Holding the monkey between the thighs of the sitting assistant as shown in Fig 1 seemed to be the best way The investigator grasped the head of the animal firmly so that the four fingers of his left hand covered the skull while the thumb was pressed under the mandible The forefinger could thus lift the right upper eyelid (Fig 2) Care was taken not to sqeeze the neck or to press on the bulb The cornea was anaesthetized with a drop of 0 4 per cent Novesine® and a fluorescein paper strip moistened in saline was placed for about 20 seconds in the conjunctival sac The IOP was determined in the right eye only because the present technique was developed for a right handed operator and the left eye was thus a more difficult problem particularly in view of the uncertainty of the reactions of the monkey After many measurements on the right eye the monkey obviously became used to the procedure and successful measurements could then be made on the left eye but these are not included in this paper

Tonometer The tonometer used was a *slightly modified version* of the hand held tonometer described by Draeger (1966) The surface of the plungertip

was reduced from 6 8 to 4 mm in diameter a size more suitable for the smaller lid fissure of the monkey although neither the applanation area of 7 35 mm (3 06 mm diameter) nor the slope of the contact surface was changed The reduction of the tip weight due to its size reduction was compensated for by adding plastic plates to both sides behind the applanation surface (Fig 3) A small sliding device was introduced by which it was possible to fade out the scale illumination and leave the light to the tip unchanged It was thus possible to perform an applanation without knowing the actual applanation force The reduced tip was calibrated in 15 eyes in live monkeys under general anaesthesia (Kaufman & Hahnenberger 1975) (CI 744 5–10 mg/kg) by open stop cock manometry Repeated application of fluorescein to the cornea soon covered it



Fig 3 1

The normal sized tip from two sides and applied to the cornea of a monkey The actual applanation surface of 3 06 mm diameter has been painted white only for illustration purposes

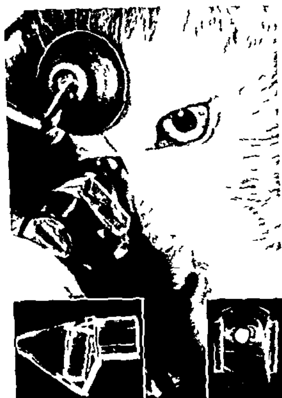


Fig 3 B
Reduced tip

with a green layer Thus only about 10–12 tonometries could be performed on any one eye at one sitting Hence measurements (2–4 applications each) were carried out at only four set pressures 10–15 mmHg apart ranging from 8 to 55 mmHg The pressures were not the same in all monkeys The reliability of the reduced tip was tested by comparing it with the normal sized tip in about 20 eyes in live monkeys under general anaesthesia. The monkeys were anaesthetized (CI 744 5–10 mg/kg b w) and tonometry was performed with the normal sized tip after 1 min with the reduced tip after a further min the normal tip and finally after yet another 1 min a second tonometry with the reduced tip was carried out. The eyes were kept open by a blepharostat throughout this testing Tonometry was continuous (see below)

Tonometry Two kinds of tonometry have been used The *continuous* (standard) method where the tip of the plunger is applied to the center of the cornea with an applanation force of 1 g This is then raised until the correct images appeared indicating an applanation area of 7 35 mm This method requires a fully trained monkey which has learned to keep eyes and head still It could not be achieved until about 10 to 14 weeks after the training had started In the beginning the *discontinuous* method had to be utilized the applanation force was set at 1 g and applied to the cornea and the position of the two half circles was quickly checked The plunger was then removed from the cornea and the applanation force increased to 1 05 g applied again the images checked and so forth This was continued until approximately 7 35 mm applanation area was achieved This method required a considerable number of applications

Drugs The anaesthetic CI 744 (Parke Davis Co) was used as a 1 per cent solution in sterile water (w/v) in a dosage between 5 and 10 mg per kg b w The drug was injected intramuscularly Novesin® in a 0 4 per cent solution was used to anaesthetize the cornea topically

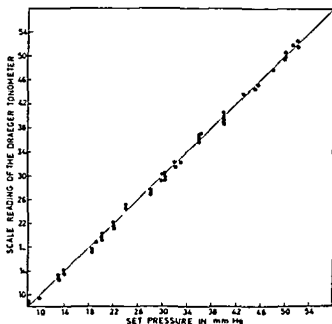


Fig 4

Open stop cock calibration in 15 live eyes between 8 and 55 mmHg Each measurement the mean of 2–4 applanation readings is represented by one point
The line represents identity

Results and Discussion

The scale readings at an applanation area of 7 35 mm in the cynomolgus monkey are very close to the set pressures (Fig 4) The applanation tonometry with the Draeger tonometer designed for human usage is thus usable in cyno molgi without any correction factor

Applanation tonometry with Goldmann type tonometer in anaesthetized owl monkeys has been reported previously Mims & Hollander (1971) used the hand held tonometer (described by Draeger) with an applanation area of 12 56 mm (4 0 mm diameter) They found a considerable deviation between actual pressure and scale reading The actual pressure and the scale reading were related as follows actual pressure = 0 641 x scale reading + 2 56 mmHg McMillan and Forster (1975) used a Goldmann tonometer but did not specify the applanation area so presumably it was 7 35 mm (3 06 mm diameter) They reported scale readings close to the actual pressures viz actual pressure = 1 04 scale reading x 10 Our observations are thus in good agreement with those of McMillan & Forster (1975) It seems that the applanation area of 7 35 mm (3 06 mm diameter) is very suitable for monkeys

Fig 5 shows that the reliability of measurements is not affected by reducing the tip size Therefore the smaller tip could also have a clinical application e g with corneal scarring or with children The IOP measured in the conscious trained monkey are listed in Table I With the first IOP measurements (about

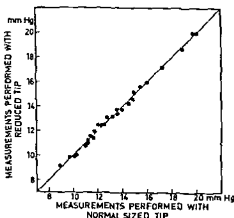


Fig 5

Comparison between the normal sized (abscissa) and the reduced tip (ordinate) in anaesthetized monkeys The line represents identity

Table I

IOP of 4 trained monkeys at the beginning of training when the discontinuous tonometry was applied (for explanation see text) and at the end of training with the continuous method (mean ± SD in mmHg). n is the number of measurements each the mean of 2–4 applications

Monkey	Beginning of training (discontinuous tonometry)	End of training (continuous tonometry)
322	$\bar{x}$ = 13.56 ± 0.86 (n = 26)	$\bar{x}$ = 18.38 ± 0.62 (n = 42)
323	$\bar{x}$ = 17.31 ± 0.64 (n = 25)	$\bar{x}$ = 22.40 ± 1.[illegible]6 (n = 42)
325	$\bar{x}$ = 12.69 ± 0.66 (n = 25)	$\bar{x}$ = 15.15 ± 0.[illegible]8 (n = 41)
304	$\bar{x}$ = 15.10 ± 1.15 (n = 25)	$\bar{x}$ = 20.4[illegible] ± 1.[illegible]5 (n = 4[illegible])
	Mean 14.7	Mean 19.12

4 weeks after actual training had started) the mean IOP of the 4 monkeys was 14.7 mmHg. After the monkey and the investigator had become completely accustomed to the tonometric procedure the IOP increased significantly with a mean value of 19.12 mmHg. These pressures then remained stable throughout the rest of the experiment and are therefore considered to be the real ones. The reason for this marked difference in IOP might be related to the way in which the tonometry was performed. In the beginning when the discontinuous tonometry had to be used the tonometer was frequently applied to the cornea. In fact a rapidly repeated tonometry was carried out and this is known to lower IOP (or at least lower the reading). Bechrakis (1966), Moses & Ching Hung (1968), Wilke (1972).

In the beginning tonometry took about 4 to 7 min whereas the whole procedure could be performed within 20 to 40 seconds once the animal had been trained. The difference between these two IOPs was about 4 to 5 mmHg with the exception of monkey 325 which displayed a difference of only 2.5 mmHg. This same monkey was the best learner and a normal tonometry performance ' be achieved with it very early on.

The investigation by Barany (1963) is the only systematic study available which screens the IOP in monkeys He performed a tonometry in supine anaesthetized (with phencyclidine) vervet monkeys with the Mackay Marg machine Although some experimental conditions were different the IOP ascertained (17 7 mmHg in average) did not differ much from the present trained value

Training monkeys is time consuming but it provides an excellent model for testing drugs which might influence the IOP and has the closest possible approximation to human conditions

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TREPHINE SECTIONS FOR CATARACT SURGERY

BY

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In 100 cases of senile cataract keratoplasty trephine was used for making lamellar cataract sections from the 3 to 9 o clock position The results are compared with sections made by keratome and scissors The advantages achieved by performing the sections with the trephine are discussed Complications due to defective wound healing are reduced to the bare minimum There was no astigmatism in 41 % of the cases The sections were ab externo enabling preplaced sutures to be inserted

Key words trephine – cataract section – astigmatism – limbus

Cataract sections are made widely with instruments such as the keratome Bard Parker knife Graefe s knife and razor blade Corneal scissors are used when the sections have to be extended

The main disadvantages of these sections is their variable degree of irregularity and the uncertainty involved in the placing of the sections resulting in an unpredictable degree of astigmatism (Kiffney & Stocker 1960 Bodian 1961 Elenius & Karo 1966 Iliff & Khodadoust 1968 Witmer & Kreinebuhul 1971 Pohjanpelto 1973) To overcome these disadvantages the Castroviejo keratoplasty trephine was used for making cataract sections

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Material and Methods

After the injection of local anaesthesia an 11 mm Castroviejo keratoplasty trephine with its obturator withdrawn 0 6 mm behind the cutting edge is placed over the upper limbus and tilted towards the operator in such a way that it is only in contact with the upper limbus The trephine is rotated between the thumb and middle finger of right hand and a lamellar mark is made in upper 180 degrees of the limbus One preplaced suture is inserted at the 12 o clock position The anterior chamber is opened with the tip of a cataract knife The section is extended with corneal scissors through the previously made lamellar incision After performing a peripheral iridectomy intracapsular lens extraction is performed The suture is tied and air is injected into the anterior chamber

This technique was used in 100 cases of senile cataract To compare the results sections were made with the keratome and scissors in a further 100 patients The patients were followed up for 6 weeks Retinoscopy was performed one week and 6 weeks after operation

Table I

Postoperative complications in cases operated on for cataract with keratoplasty trephine sections

Complication		Number of cases
Iris prolapse	first postoperative day	nil
	third postoperative day	-
Hyphaema	mild	2
	severe	nil
Iris prolapse		
+	first postoperative day	nil
Hyphaema	third postoperative day (traumatic)	1
Wound ectasia		1
Striate keratitis	mild	4
	moderate	-
	severe	nil
Collapsed anterior chamber	till third postoperative day	

Table II

Astigmatism 1 week postoperatively in cases with trephine sections

Cylindrical correction	Type of astigmatism				Total
	Spherical	With rule	Against rule	Oblique	
0	[illegible]	–	–	–	17
0.25–1 D	–	3	15	0	18
1.25–2 D	–	9	11	2	[illegible]
2.25–3 D	–	11	3	0	14
More than 3 D	–	22	5	2	29
Total	[illegible]	45	34	4	100

Results

In the postoperative period the patients were examined for any complication arising as a result of defective wound healing such as a ragged or leaking wound shallow or collapsed anterior chamber iris prolapse or hyphaema. The *encountered complications are listed in Table I Observations on the behaviour* of astigmatism in cases where the sections were made with the trephine are

Table III

Astigmatism 6 weeks postoperatively in cases with trephine sections

Cylindrical correction	Type of astigmatism				Total
	Spherical	With rule	Against rule	Oblique	
0	41	–	–	–	41
0.25–1 D	–	[illegible]	19	1	[illegible]
1.25–2 D	–	[illegible]	[illegible]	1	[illegible]
2.25–3 D		0	4	0	4
More than 3 D	–	0	0	0	0
Total	41	9	45	2	[illegible]

Table IV
Behaviour of astigmatism from 1 to 6 weeks postoperatively in cases with trephine sections.

Nature of astigmatism one week postoperatively		Nature of astigmatism six weeks postoperatively			
Type of astigmatism	Cases	Spherical	With rule	Against rule	Oblique
Spherical	17	8	3	6	0
With rule	45	17	0	28	0
Against rule	34	14	6	14	0
Oblique	4	2	0	0	2
Total	100	41	9	48	2

given in Tables II–IV. Spherical corrections alone were observed in 41 % of the cases with trephine sections and 21 % of the cases with keratome sections ($P < 0.05$).

Discussion

The position and the regularity of the cataract section are two factors of utmost importance for the ocular behaviour in the postoperative period. With the usual methods of performing cataract sections both of these factors are most unpredictable. The *disadvantages are overcome by making the sections* with the keratoplasty trephine. The sections are not only regular, smooth and sharp but also slightly oblique due to the tilt given to the trephine. The sections are ab externo where preplaced sutures can be inserted enabling accurate edge to edge apposition of the wound. Crushing of the tissues by the scissors is minimized as the section has previously been partially completed. This markedly reduces the chances of complications and the degree of astigmatism. By means of the new technique, no astigmatism was observed in 41 % of the cases, whereas with other methods it has been found in 14 % and 22 % (Kiffney & Stocker 1960), 15 % (Bodian 1961), 17 % and 22 % (Pohjanpelto 1975) and 21 % of our own cases.

When the keratoplasty trephine is used for making cataract sections not

only the sclerocorneal junction but also the conjunctiva is incised The con junctiva can be easily retracted while placing the sclerocorneal suture. This avoids its inclusion into the wound edges Bleeding while making the section is minimal as the sections are limbal Striate keratitis is negligible because of the proper edge to edge wound apposition and the least possible crushing of the tissues

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STATIC PERIMETRY STRATEGIES

BY

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JÖRG SPAHR

In static perimetry the method of limits is widely used for threshold determinations Its performance is compared with that of a certain modification of the staircase method (repetitive up and down method) by means of simulations where the behaviour of the observer is described by an assumed psychometric function Systematic and random errors are considerably smaller with the up and down method. Further consideration is given to signal detection theory and to the concept of optimal strategy

Key words perimetry static – visual field

The purpose of a static visual field examination is primarily to establish the contrast sensitivity for a large number of retinal points at a defined background luminance spot size and exposure duration. In this paper we are essentially concerned with the methodology of measurement procedure and with the question of reliability and reproducibility of measured results in the framework of different strategies of static perimetry This subject is an entity in itself and does not necessarily include discussion of distinguishing criteria for the existence of pathological behaviour Generally speaking the focus is on the patient as an observation system with statistically describable proper

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ties and the optimization of measurement methodology exclusively in relation to the primary measurement of threshold values

Since the responses of the patient include random components and since the characteristic parameters of the observer system vary from person to person and are not generally predictable it is necessary to apply statistical concepts. This applies both to the construction of models and to the analysis of measured results obtained from repeated use of one or more methods on different persons To be more specific the questions involved are of the following type

What is the accuracy of a single measurement?

According to which criteria may the different methods of static perimetry be compared (e g method of limits and staircase method)?

What is the optimal examination strategy in relation to the maximum gain of information or in other words how can the most accurate results be obtained for any given effort?

The problem of optimal examination strategy has already been solved by Spahr (1975) whose essential results will be summarized

In spite of general prejudice we emphasize that computer simulation for selected problems concerning perimetric measurement techniques may be a conclusive method If for example we accept that an individual frequency of seeing curve adequately reproduces the distribution of the seen/not seen response of a given person as a function of the intensity of the stimulus at a given point of the visual field there can be no doubt that a computer simulation can compare the different techniques of measurement (e g method of limits and staircase method) It must however be admitted that some other components are not taken into account in simulations as for example differential levels of attentiveness due to different interrogation methods Evidently in numerical simulations the relevant parameters of the observation system must be stated (in this case the parameters of the frequency of seeing curve) or better still the distribution of these for a group of subjects

We limit our analysis to yes no procedures *i e* the subject reports during a limited time interval whether he has perceived a stimulus The absence of a seen response is interpreted as not seen

The Psychometric Function

The frequency of seeing curve for a subject (valid for a specific retinal point) as a function of the logarithm S of the stimulus luminance represents the probability p(S) of perception. Parameters such as spot size duration of exposure and background luminance are constant Qualitatively p(S) is represented by a monotonic increasing

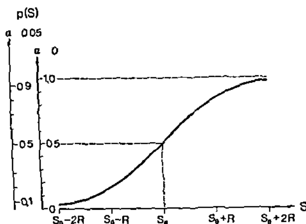


Fig 1
The psychometric function. S is the logarithm of stimulus luminance. S threshold p(S) detection probability R a parameters (see text)

function which increases from $p \simeq 0$ to $p \simeq 1$ in an interval $S - R < S < S_o + R$. It suffices to represent p(S) by two parameters where S represents the threshold stimulus i e. that stimulus which is perceived with the probability $p = 0.5$ $(p(S_o) = 1/2)$ while the second parameter R specifies the order of magnitude of the increase of the stimulus above threshold that is required to make the probability of perception almost one.

It is well known that measured p(S) curves can be approximated in different ways by simple functions In relation to classical models p(S) is often expressed as a cumulative normal distribution

$$p(S) = \int_{-\infty}^{S} dS \frac{1}{R\sqrt{2\pi}} e^{-(S-S_o)^2/2R^2} \qquad (1)$$

This function is represented in Fig 1 and has the quality described above, in particular $p(-\infty) = 0$ $p(S_o - R) = 0.16$ $p(S_o) = 1/2$ $p(S_o + R) = 0.84$ $p(\infty) = 1$ The scale of the parameter R was arbitrarily chosen and p increases from a value of 0 16 at S_o R to 0 84 at $S_o + R$ (mathematically R was introduced as the standard deviation of the normal distribution in the integrand of (1))

If (1) is taken as an approximation of a measured p(S) further confirmation is unnecessary However the use of the parameters in (1) and the significance of R become distinctly clearer when considered in the light of the following derivation from a classical threshold model A momentary threshold S at the instant of a stimulus i shall be composed of a constant mean threshold S and a normally distributed random number R_i with mean zero and standard deviation R. Furthermore, a seen response shall occur exactly when the stimulus exceeds the momentary threshold value S Equation (1) then follows directly without further assumptions

Since the temporal behaviour of thresholds exhibits short and long term fluctuations, the definition of R is somewhat ambiguous. As a matter of definition we derive the frequency of seeing curve and the corresponding numerical value of R from a yes-no pattern observed within a relatively short time interval (e.g. 15 min).

The numerical value of R varies from person to person. In a sample of 16 normal and pathological visual fields of untrained subjects values between 0.9 dB and 4 dB (1 dB = 0.1 l.u.) were obtained. Similar values are given in the literature (see e.g. Roufs 1974). If considered strictly, R may vary with the location on the retina. Fankhauser et al. (1966) reported a local increase of R with density of defect in a case of chorioretinitis juxtapapillaris. However, in the analysis of eight other pathological visual fields such a correlation was observed in one case only. In the following R is assumed to be an individual parameter, independent of location on the retina and essentially determining the exactitude with which the threshold can be ascertained under similar conditions.

For numerical simulations the following approximation of (1) is quite suitable:

$$p(S) = \left\{1 + e^{-1.81 (S_0 - S)/R}\right\}^{-1} \qquad (2)$$

The factor 1.81 guaranties a fairly good correlation between (1) and (2). In fact, the deviation of the ordinates is in any case less than 0.02. (dp/dS is according to (1) a normal distribution with a standard deviation of R; the standard deviation of the derivative of (2) has the same value to within about 1 %.)

In reality, the probability of perception p even for extremely strong stimuli (30 dB above threshold, e.g.) does not attain the value 1. On the other hand, the subject may also produce a 'seen' response when no stimulus existed. For the sake of simplicity in our simulations we assume both effects (fraction of non-recognized strong signals and fraction of false alarms) to be equal and call this fraction α. In order to account schematically for both effects we generalize (2) as follows:

$$p(S) = \alpha + (1-2\alpha)\left\{1 + e^{-1.81 (S_0 - S)/R}\right\}^{-1} \qquad (3)$$

The probability of perception no longer increases from 0 to 1 but *from α to 1-α*. According to our experience, for most untrained subjects α lies between 0.01 and 0.05. In simulations we work with values $\alpha = 0$ and $\alpha = 0.05$. For these cases the numerical values of p(S) are given in Fig. 1.

So far we have characterized the observation system (at a specific retinal point) by means of a function and its parameters. The receiver operator characteristic (ROC) has not been mentioned, although much space is devoted to it in signal detection theory (Green & Swets 1966, Nachmias 1972). In effect, the threshold S_0 and the fraction of false alarms do not only depend on the physical conditions of the system and the external physical parameters (exposure time etc.) but also on the momentary attitude of the patient, and therefore on the instructions of the investigator. The willingness to give a 'seen' reaction to a barely perceptible impression is subject to manipulation and can vary from one examination to another. However, accounting for this cognition of signal detection theory is beyond the practical possibilities of perimetric investigation. The determination of a patient's momentary condition would mean, in general terms, that at least the fraction of false alarms relative to the non-existence of certain expected stimuli would have to be retested before each examination.

The following numerical example illustrates clearly that the necessary effort far exceeds the practical possibilities Let α be of the order of magnitude 0 05 For 100 missing stimuli in a larger number of observational intervals one would expect $5 \pm \sqrt{5}$ false alarms A conclusion drawn from the sampled number of false alarms is therefore fraught with an uncertainty of the order of 50 % *(in spite of a far too great investment)* In practice, we must simply rely on the patient s ability to maintain his decision criteria, assisted as far as possible by the most uniform instruction Random variations in the decision criteria over a long period of time should appear as long term fluctuations in the thresholds Later on, we resolve the fluctuations into short and long term components where it will be shown that long term fluctuations are in effect relatively small and for the root mean square value of the order of 1 to 2 dB (Bebie Fankhauser & Spahr 1976)

Strategies

The primary object of static perimetry consists in achieving an accuracy of the order of magnitude of 2 dB within a reasonable time of observation The present study concerns an investigation of methods of measurement which are particular to the automaton OCTOPUS (Spahr 1973 Spahr & Fankhauser 1974a)

Fixation stability is controlled by the perimetrist or an automated system

Each stimulus consists of a short presentation of a test mark

Location and intensity of the stimulus are not predictable

The projection of a stimulus is either announced or can be expected periodically

The patient should signal the perception of a stimulus This signal is counted as a seen response (A = 1) the absence of a signal constitutes a not seen response (A = −1)

Within the totality of all stimuli in a single complete examination of the visual field we concentrate on the time ordered series S_1 S S_N of those stimuli presented at a given point of the visual field (interspersed with stimuli at other points which we ignore) as well as the corresponding series of responses A_1 A A_N These values provide the basic data for the method of approximation of the threshold S at the given point of the visual field In case S_0 is determined several times independently at one and the same point in the course of the same session only one such determination will be analyzed in the following

The problem which must be considered in the search for a good strategy is as follows according to which rules must the stimuli be chosen so that either an optimal information gain per answer is obtained or so that the

spread of the results of repeated threshold determinations (at a given retinal point) becomes as small as possible for a given number of stimuli per determination? Applying basic concepts of mathematical information theory information gain is a well defined quantity Intuitively both criterias are almost equivalent The principle of optimal information gain has been applied by Spahr (1975) in order to derive the rules of the optimal strategy In section 4 two selected strategies will be compared relative to the spread of results of repeated threshold determinations

In order to deal mathematically with such problems two types of assumptions must be made

Let the behaviour of the subject be described by a psychometric function (3) with unknown threshold S_0 where for the purpose of model investigations the parameters R and α describing the subject s behaviour are assumed to be given

The preliminary knowledge relating to the threshold to be determined must be circumscribed statistically For a first examination the best pre knowledge consists of the probability distribution $w_0(S_0)$ of the thresholds S at given coordinates of the visual field for the age group to which the subject belongs This distribution is empirically known and can be represented with the assumption of normal distribution through the mean $< S_0 >$ (for the given age group and at a given retinal location) and the standard deviation ΔS $< S >$ is of course dependent on exposure time (if smaller than the critical time) spot size (if smaller than the summation area) background luminance and age In addition the origin of the scale varies from one perimeter type to another ΔS the interindividual standard deviation for a given age group is almost independent of age and is roughly 2 dB for a population with normal visual fields (Aspinall 1967) Verriest & Israel (1965) found $\Delta S = 1$ dB at the centre and $\Delta S_0 = 2$ dB at the periphery Greve & Wijnans (1973) obtained values increasing from 0 6 dB at the centre to 1 6 dB at the periphery (For a population with pathological visual fields ΔS might rise to about 4 dB or even more at a rough guess However it will be possibly to proceed from better pre knowledge for repeated examinations)

In the next section we will be concerned with the analysis of the following two strategies a) and b) Method a) is widely used in clinical visual field examinations whereas our interest in method b) derives from the fact that it is a very good approximation to the optimal strategy (Spahr 1975)

a) Method of limits

It consists of an ascending series $S_1 < S < S_3 <$ of stimuli originating at an infraliminal level S_1 until a stimulus S_X is perceived S_X (or perhaps the

mean between S_N and S_{N-1}) is then taken as result s of that determination of S. The first stimulus is chosen for example about 2–4 dB below the mean threshold for the corresponding age group (at the given retinal point). In particular the increase of stimulus intensity can be achieved at constant intervals Δ: $S_n = S_1 + (n-1)\Delta$ where Δ can be for instance 2 dB or 4 dB. Such a one sided approach is implicit in the instructions for use of the Friedmann analyser regardless of the suggested modifications also mentioned in these instructions.

b) Repetitive up and down method

This method which is almost optimal operates according to the following rules (Spahr 1975):

(i) The mean $\langle S_o \rangle$ of the thresholds for a given age group at a given retinal point is chosen as a first stimulus S_1.

(ii) If the first stimulus meets with no response ($A_1 = -1$) the next stimulus is increased by 4 dB, otherwise ($A_1 = +1$) it is reduced by 4 dB.

$$S_2 = S_1 - A_1 \cdot 4\ \text{dB} \qquad (4)$$

Generally if a positive response is obtained the stimulus is diminished or otherwise augmented.

(iii) Following a response A_n to a stimulus S_n ($n \geq 2$) the next stimulus S_{n+1} is chosen according to

$$\text{case 1: } A_n \neq A_{n-1}: \quad S_{n+1} - S_n = -\tfrac{1}{2}\,(S_n - S_{n-1})$$
$$\text{case 2: } A_n = A_{n-1}: \quad S_{n+1} - S_n = S_n - S_{n-1} \qquad (5)$$

(iv) That stimulus S_N for which according to the previous pattern a correction of only 1 dB should follow is the last. The correction of 1 dB is a calculated one and the result is taken as

$$s = S_N - A_N \cdot 1\ \text{dB} \qquad (6)$$

To illustrate (iii) first case (seen follows not seen or the reverse) it is assumed with a reasonable probability that the transition from S_{n-1} to S_n has exceeded the threshold. It is therefore reasonable to attempt the next correction ($S_{n+1} - S_n$) with reversed sign and reduced to one half of the preceding correction step ($S_n - S_{n-1}$) as is usual in binary bracketing strategies. However in case the response of the subject does not alter (case 2, e.g. in case after a not seen response for the stimulus S_{n-1} another not seen follows for a stronger stimulus S_n) it is probable that the threshold was not exceeded. Therefore the same correction is once again applied (in view of a possibly distant threshold) without reducing the step size. As a result of these rules a series of corrections of 4 dB, 2 dB, 1 dB succeed each other. It is possible that the same correction occurs several times (except the last correction 1 dB) hence the term repetitive up and down method (or symbolically method 4 – 2 – 1).

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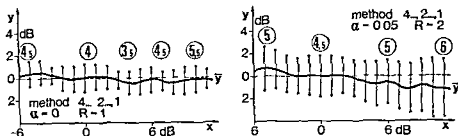


Fig 2

Distribution of the results of repeated determination of the same threshold S_0 $x = S$ S_1 position of the first stimulus S_1 relative to the true threshold ($x > 0$ infraliminal first stimulus) $y = s$ S_0 position of a result s relative to the true threshold y (extended line) systematic error Vertical bars random error (± 1 SD) Left half good observer Right half less reliable observer Method repetitive up and down 4 2 1

smaller they are the better the reliability of a single threshold determination and the better the strategy This program may either be carried out with real observers or by means of computer simulations in which case the behaviour of the observational system is described by an assumed psychometric function Once the strategy is given the parameters R and α of the psychometric function the true threshold S_0 (defined through $p(S_0) = 1/2$ in the assumed psychometric function) and the first stimulus S_1 the distribution of the results s of repeated measurements is determined uniquely

The numerical results were obtained from both analytical considerations and from numerical simulations and are given in Figs 2 3 and 4 Fig 2 was obtained from the repetitive up and down method 4 2 1 Fig 3 from the method of limits with intervals $\Delta = 4$ dB Fig 4 from the method of limits with intervals $\Delta = 2$ dB The figures on the left hand side refer to the model of a good observer ($R = 1$ $\alpha = 0$) and those on the right hand side to an observer with an unfavourable psychometric function ($R = 2$ $\alpha = 0\ 05$) The abscissa is chosen to be $x = S_0 - S_1$ (position of the first stimulus relative to the true threshold in dB) Therefore if for example $x = 12$ this will imply that the first stimulus is infraliminal by 12 dB resulting perhaps from serious depression of sensitivity at a given point The results of measurement relative to the true threshold ($y = s - S$) are marked vertically the extended curve represents the mean $y = \bar{s} - S$ (systematic error) and the vertical bars symbolize the spread of the distribution of the results of measurement (± 1 SD i e $\pm\ \sigma$) Note that exact measurements would yield the horizontal $y = 0$ The circled numbers are the average number of stimuli used dependent on x

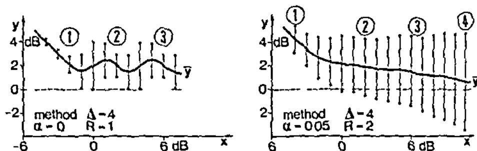


Fig 3
Same as Fig 2 – Method of limits step size $\Delta = 4$ dB

Comparison of Figs 2 3 and 4 leads to the following conclusions

Repetitive up and down method as an average of repeated measurements yields the true threshold with great accuracy This is quite independent of whether the first stimulus was infra or supra liminal The deviation of measurements depends very little on the relative location of the first stimulus to the true threshold and is therefore almost independent of the density of defect (evidently on the assumption that parameters R α of the psychometric function are not affected by functional losses)

The method of limits is significantly more problematic It does not yield the true threshold as an average of repeated measurements Specifically there is a dependence between the systematic error $\bar{y} = s - S$ and the location of the first stimulus relative to the true threshold In so far as the first stimulus is infraliminal ($x > 0$) and is always applied according to the same rules this difficulty does not have too far reaching consequences The effect can be taken simply as a systematic scale transformation which is reproducible

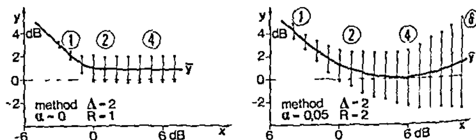


Fig 4
Same as Fig 2 – Method of limits step size $\Delta = 2$ dB

for repeated measurements (under the defined conditions) However for first stimuli in the region of the true threshold or even supraliminal the method of limits is relatively useless and the small deviation σ of the measurements should not be misinterpreted since the probability of a seen response to a first stimulus is considerable the first stimulus will in all probability be perceived and thus produce a large systematic error $\bar{y}$ in the region of $x < 0$ Since this seen response is probably reproducible for repeated measurements the spread of these results is negligible However such a response has very little value because little information has been obtained as to the true location of the threshold and nothing has been learned about possible early functional losses (In careful visual field examinations by means of the method of limits this difficulty is usually avoided by rejecting a positive first answer and damping the stimulus until an approach from the infraliminal side becomes possible)

The average number of stimuli needed for the up and down method is greater than that for the method of limits This is the price paid for the greater reliability of bracketing results

The reliability of threshold determinations may be increased by operating the up and down method with correction steps 2 1 ½ instead of the steps 4 2 1 used in the derivation of Fig 2 In fact further simulations have shown that σ would be reduced to about 80 % of the values shown in Fig 2 On the other hand the number of stimuli rises slightly (about 4 5 stimuli for $x = 0$ and about 6 stimuli for $x = 6$)

Heijl & Krakau (1974 1975a b) have investigated a similar up and down procedure based, however on correction steps of constant size. For a step size of 3 dB (Heijl & Krakau 1975b) the performance of their strategy comes rather close to the one given in Fig 2 for the method 4 2 1 – A comparison with other strategies has been outlined elsewhere (Spahr & Fankhauser 1974b)

Finally we restrict ourselves to the up and down method 4 2 1 and consider in more detail the dependence of the mean error of single threshold determinations on the parameters R and α of the psychometric function According to Fig 2 the systematic error $\bar{y}$ may be neglected and $\sigma = \sigma(x\ R\ \alpha)$ is only slightly dependant on x In Fig 5 the dependence of σ on R and α is given (To be more precise the values of σ given in Fig 5 were obtained through a calculated average of $\sigma = \sigma(x\ R\ \alpha)$ over a normal distribution of x with mean zero and a standard deviation Δx of 2 dB according to the inter individual variability $\Delta S = 2$ dB valid for normal visual fields For a set of pathological visual fields $\Delta x = \Delta S = 4$ dB might be appropriate However due to the weak dependence of $\sigma(x\ R\ \alpha)$ on x the values of σ (Fig 5) are increased by a few per cent only)

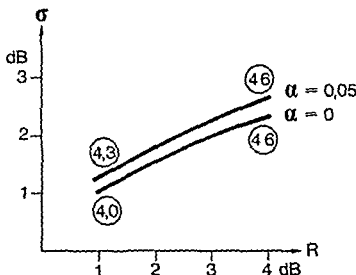


Fig 5

Dependence of the error σ of single threshold determinations upon the parameters R α of the psychometric function Method repetitive up and down 4 2 1
Circled numbers average number of stimuli per determination

We have determined σ for a sample of 16 normal and pathological visual fields of untrained subjects (repetition of measurements within 15 min method 4 2 1) Individual values of σ ranged from 0 8 dB to 3 5 dB (mean 1 8 ± 0 8 dB) Details will be given in a subsequent paper (Bebie Fankhauser & Spahr 1976)

The Optimal Strategy

In the case of an *ideal observer* whose psychometric function is of the form

$$p(S) = \begin{cases} 1 & S > S \\ 0 & S < S_o \end{cases} \qquad (7)$$

with unknown threshold S the establishment of an optimal strategy is unproblematic. The gain of information takes on the optimal value of exactly one bit per answer when the stimuli are chosen in such a way that yes and no responses can be expected with equal probabilities (0 5) for each stimulus When this principle is applied to a normally distributed pre knowledge described by the mean threshold $< S_o >$ (for the given age group and retinal location) and the interindividual standard deviation ΔS_o as mentioned in section 3 the following stimuli are obtained

$$S_1 = \langle S_0 \rangle \qquad \rightarrow \text{answer } A_1$$

$$S_2 = \begin{cases} \langle S_0 \rangle - 0.68\,\Delta S & \text{if } A_1 = 1 \\ \langle S_0 \rangle + 0.68\,\Delta S & \text{if } A_1 = -1 \end{cases} \qquad \rightarrow \text{answer } A_2$$

$$S_3 = \begin{cases} \langle S_0 \rangle - 1.15\,\Delta S_0 & \text{if } A_1 = 1 \quad A_2 = 1 \\ \langle S_0 \rangle - 0.32\,\Delta S & \text{if } A_1 = 1 \quad A_2 = -1 \\ \langle S_0 \rangle + 0.32\,\Delta S_0 & \text{if } A_1 = -1 \quad A_2 = 1 \\ \langle S_0 \rangle + 1.15\,\Delta S_0 & \text{if } A_1 = -1 \quad A_2 = -1 \end{cases} \qquad \rightarrow \text{answer } A_3$$

Note that these points divide the area under the normal distribution with mean $\langle S_0 \rangle$ and s d ΔS into eight equal parts which quaranties the equal probability of all the possible combinations of responses Therefore *for $\Delta S_0 = 2$ dB (normal visual fields)* a first correction step of less than 2 dB would be appropriate for pathological visual fields assuming e g $\Delta S_0 = 6$ dB the first correction step should be of the order *of 4 dB Should one be prepared to accept the ideal observer as a standard* these two examples illustrate the criterium for the practical choice between the up and down methods 4 2 1 and 2 1 [illegible]

For real observers ($R \neq 0$ $\alpha \neq 0$) the *optimal strategy* has been fully investigated by Spahr (1975) who applied principles of mathematical information theory in order to obtain optimal information gain per response The pattern of stimuli follows more complicated rules However some of the main results may be summarized as follows

The optimal strategy exists i e the stimuli follow uniquely from R α, the previous responses and the statistical description of the pre knowledge

Information gain drops to about 0.5 bit per response

The first correction interval should be about two thirds of ΔS_0

The repetitive up and down method is a very good schematic approximation of the more complicated rules of the optimal strategy In fact, the gain of information per response is percentually only slightly below that of the optimal strategy The accuracy of single threshold determinations in both cases (optimal strategy repetitive up and down method) is almost identical

Zusammenfassung

Mithilfe von Simulationen werden zwei Schwellenbestimmungsmethoden der statischen *Perimetrie bezüglich der Genauigkeit der Messresultate verglichen*, und zwar die Methode der einseitigen Schwellenannäherung vom unterschwelligen Bereich her mit einer Modifikation der staircase – Methode so wie sie auf Automaten zur Anwendung kommen *kann. Die Messfehler fallen bei der zweiten Methode wesentlich kleiner aus* Weitere Betrachtungen beziehen sich auf die Signaldetektionstheorie und auf den Begriff der optimalen Strategie.

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STATIC PERIMETRY ACCURACY AND FLUCTUATIONS

BY

HANS BEBIE FRANZ FANKHAUSER and JÖRG SPAHR

Threshold fluctuations are divided into short term and long term effects applying statistical methods Sixteen normal and pathological visual fields were analysed in order to obtain the numerical values for the short term long term and total fluctuation Special attention is paid to fortuitous variations between the results obtained at successive examinations Finally the concept of spatial correlations is introduced

Key words perimetry static – visual field

In this study an attempt will be made to analyse the intraindividual threshold fluctuations with regard to a discussion of the accuracy and reliability of static visual field examinations In a previous publication two different methods of static perimetry were compared with respect to the spread σ of the results of repeated threshold determinations or in other words with respect to the accuracy of single measurements (Bebie Fankhauser & Spahr 1976 it is assumed that the reader is familiar with the notations of that paper which will be referred to as I) By definition these independent repetitions were assumed to be carried out under the same conditions (same subject or psycho

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metric function same retinal location same method of threshold determination) Furthermore repeated measurements of the same threshold took place within a relatively short time interval e g 15 min. In simulations this restriction was introduced through a corresponding definition of the frequency of seeing curve

According to this confinement to short intervals of observation the individual parameter σ (which was fully discussed in I and which was defined as the standard deviation of the distribution of the results of repeated determinations of the same threshold) is due to short term fluctuations (In the terminology of a classical threshold model the short term fluctuations of the threshold itself are described by the parameter R of the psychometric function) It is known however that thresholds are liable to reversible long term fluctuations which although they have a random character remain constant within one session (of 15 min duration) and within the framework of our definitions and therefore do not influence σ At a later examination after days or weeks these slower alterations become apparent and increase the total spread of results (Henceforth result is to be undersstood as the result of a threshold determination)

In a rigorous mathematical treatment all possible frequencies of fluctuations would have to be taken into account i e the threshold at a specific retinal point would have to be considered as a stochastic function of time subject to spectral analysis (Krakau 1969 Ronchi 1972 Ronchi et al 1974) For the purposes of practical perimetry it appears to us that a drastically simplified description of the spectrum suffices i e a resolution into short term and long term fluctuations within the context of these simplifications we assume that the long term fluctuations do not depend upon the time intervals between successive sessions In section 2 the long term fluctuations will be characterized by their root mean square value σ_L the standard deviation of the results (for a given subject and at a specific retinal point) sampled over two more sessions covering a period of days weeks or months will then be given by

$$\sigma_{t\,t} = \sqrt{\sigma + \sigma_L} \quad (1)$$

The intraindividual variation σ which characterizes the ability of the subject to reproduce the same threshold (in independent repetitions of the measurement carried out within the same session) is different for each subject. The same remark applies to $\sigma_{t\,t}$ which may be interpreted as the intraindividual variation found by comparing the results of two examinations separated by an interval of days. weeks or months.assuming that there are no pathological changes. We shall assume that σ (as well as σ_L and $\sigma_{t\,t}$) is independent of retinal location The lowest value found in the analysis of 16 visual fields

Table I

Intra individual threshold fluctuations of untrained subjects

		σ	L^{I}	L^{II}	σ_L	σ_{tot}	
F W	os	2.5	0.0	1.6	1.6	2.9	p
F W	od	1.3	1.1	0.2	1.2	1.7	p
O H	os	0.9	0.6	0.1	0.6	1.1	p
O H	od	1.4	0.4	0.5	0.6	1.6	p
O N	os	0.8	0.6	0.0	0.6	1.0	p
O N	od	0.9	0.2	0.2	0.3	0.9	p
M J	os	3.5	2.7	3.2	4.2	5.4	p
M J	od	2.6	1.1	2.7	2.9	3.9	p
G B	os & od	2.5				4.5	p
E Sch	os & od	1.1				1.2	n
M H	os & od	1.7				2.0	n
M W	os & od	1.2				1.2	n
H S	os	2.6	1.8	3.0	3.5	4.4	n
T W	os	2.0	2.2	1.3	2.6	3.3	n
A B	os	1.7	0.5	1.5	1.6	2.3	n
E M	os	1.7	0.7	0.7	1.0	2.0	n
mean ± 1 s d		*1.8±0.8*	*1.0±0.8*	*1.3±1.2*	*1.7±1.3*	*2.5±1.4*	

σ short term fluctuation, σ_L long term fluctuation L^{I} synchronous component of long term fluctuations L^{II} uncorrelated component of long term fluctuations σ_{tot} total fluctuation (r m s values in dB 1 dB = 0.1 log unit) p pathological visual field n normal visual field

was $\sigma = 0.8$ dB whereas the highest was above 4 dB σ_{tot} was found to exceed σ by about 40 % (mean value for details see section 2 and Table I)

In judging the reliability of the results of a visual field examination or in judging the significance of temporal changes encountered during the course of a few months e g the σ_{tot} of the subject ought to be known However since the individual value of σ_{tot} is in general not significantly larger than σ alone, and since both follow the same trend σ may also be used in order to classify the reliability of a subject We propose to use σ (which may easily be determined within one session as will be shown in section 3) as an individual index of reliability

Note that σ depends on the method of threshold determination as was

pointed out in I whereas σ_L and R are independent of this factor Our results were obtained from the repetitive up and down method 4 2 1 (Spahr 1975)

Short term and Long term Fluctuations

Let s(n j) denote the results of repeated threshold determinations (for a given subject and at a specific retinal point) A session lasts at most 15 min and the threshold is determined N times per session (n = 1 N) there are J consecutive sessions at intervals of days or weeks (j = 1 J) The mean of the jth session is denoted by s(O j) the mean of all sessions by s(O O)

$$s(O\ j) = N^{-1} \sum_{n} s(n\ j)$$

$$s(O\ O) = J^{-1} \sum_{j} s(O\ j) \qquad (2)$$

The single result s(n j) is decomposed according to the definition of short term and long term fluctuations as follows

$$s(n\ j) = S_o + A_{nj} + B_j \qquad (3)$$

S_o is the unknown threshold Statistically independent random numbers A_{nj} represent the short term fluctuations where the mean is zero and the root mean square value is given by σ independent random numbers B_j *correspond* to the long term fluctuations and by definition they do not depend on n their mean value vanishes and the root mean square value is equal to σ_L

$$< A_{nj}^2 > = \sigma^2 \quad < B_j^2 > = \sigma_L^2 \qquad (4)$$

The derivation of the formulas for the determinations of σ and σ_L from a set of data s(n j) is straight forward and no assumptions are necessary From elementary statistics the sample estimates for σ and σ_L are obtained as follows

$$\sigma = \left\{ J^{-1}(N-1)^{-1} \sum_{j\,n} [s(n\ j) - s(O\ j)]^2 \right\}^{1/2} \qquad (5)$$

$$\sigma_L = \left\{ (J-1)^{-1} \sum_{j} [s(O\ j) - s(O\ O)]^2 - N^{-1}\ \sigma^2 \right\}^{1/2} \qquad (6)$$

To interprete the first of these formulas the fluctuations within one session are computed and averaged over all sessions in order to give the final estimate for the r m s value of the short term fluctuations Note that the long term fluctuation is not as might be expected equal to the fluctuation of the average results $s(O\,j)$ Due to the influence of short term alterations the $s(O\,j)$ would deviate even in the extreme case $\sigma_L = 0$ This effect is taken care of by the second term on the right hand side of eq (6)

Using (5) (6) and (1) we obtained the numerical values of σ σ_L and $\sigma_{t\,t}$ for a number of untrained subjects (10 to 70 years of age) with normal and pathological visual fields summarized in Table I

The rough data $s(n\,j)$ were obtained through the repetitive up and down method on the automaton OCTOPUS (Spahr 1973 Spahr and Fankhauser 1974 1975) Measurements were simultaneously made for several points of the visual field (central and peripheral during sessions of about 15 minutes duration) Data given in Table I represent a squared average over a minimum of eight retinal points The number J of sessions was from two to four with roughly a two week time interval between the first and last examination The number N of independent determinations of a threshold per session and per location was generally five so that the data is based on approximately 100 to 200 static measurements per subject Background luminance was 4 asb exposure 200 msec spot size 0 43° Fixation was strictly controlled

The contents of Table I may be summarized as follows

The r m s value σ of the short term fluctuations lies between 1 dB and 4 dB their distribution has a mean of 1 8 dB and a standard deviation of 0 8 dB

The *short term fluctuation must* be *increased* by *about* 40 % *in order to* obtain the subject s total fluctuation $\sigma_{t\,t}$ The average of $\sigma_{t\,t}$ over our 16 visual fields is 2 5 dB which is surprisingly high. It is probable that $\sigma_{t\,t}$ would be even greater if it were derived from data covering a period of several months instead of only two weeks An improvement of the empirical foundation in this question is to be desired

It is supposed that the long term fluctuations are composed of two parts a first component is independent of retinal location and affects the thresholds of all points simultaneously whereas a second component is statistically independent for all points of the visual field Let the r m s value of the systematic part (common to all locations of the visual field) be denoted by L^I and the r m s value of the remaining part (varying *with location) by* L^{II} *For the result* $s(n\,j\,k)$ *which refers to the nth determination* during the jth session at a retinal point k (k = 1   K) the generalization of (3) and (4) reads

$$s(n\,j\,k) = S + A_{jk} + B^{I}_{j} + B^{II}_{jk} \qquad (7)$$

$$\langle A_{jk} \rangle = \sigma \quad \langle (B^{I}_{j}) \rangle = L^{I} \quad \langle (B^{II}_{jk}) \rangle = L^{II} \qquad (8)$$

where the right hand side of (7) consists of the sum of the threshold and random numbers vanishing in the mean and being independent of each other The numerical

decomposition of the long term fluctuation σ_l into its components L^I and L^{II} is given in Table I as obtained from the data mentioned above Obviously the systematic component L^I is of no significance compared to the total fluctuations Making the tempting correction to eliminate B^I_j after each session for equal spatial mean is therefore of no interest quite apart from the fact that this could lead to masking of systematic and irreversible changes From these considerations we abandon the resolution of the long term fluctuation into its components

To conclude the repetition of a perimetric examination (for example after six months) will always exhibit certain variations in the results These can have two independent causes

(i) Incidents in the scope of the usual spread of the results obtained from single threshold determinations (because of the non ideal character of the psychometric function and the resulting fortuitousness of patient responses and because of reversible long term fluctuations) the scale being given by the subject s $\sigma_{l\,t}$

(ii) Pathological changes

We should like to point out that fortuitous alterations are quite frequent to the extent of $\sigma_{l\,t}$ or even $2\ \sigma_{l\,t}$ Let s be the result of a first threshold determination and s that of a succeeding examination at a given retinal point Assuming that there are no pathological changes an apparent detoriation $s\ s \geqq \lambda$ will be encountered with a probability $q(\lambda)$ at the given retinal point From elementary statistics one obtains $q(\lambda = \sigma_{tot}) = 0\ 24$ and $q(\lambda = 2\ \sigma_{l\,t}) = 0\ 08$ assuming a normal distribution of the differences s s The following example may illustrate these figures Let $\sigma_{l\,t} = 2$ dB which is a moderate value and assume that threshold determinations have been carried out at twelve retinal points (i e twelve single measurements at a first examination and twelve single measurements at a subsequent examination weeks or months later) An apparent detoriation to the extent of 2 dB or more ($\lambda = \sigma_{l\,t}$) may then be expected at three points whereas a detoriation of 4 dB or more ($\lambda = 2\ \sigma_{l\,t}$) may be encountered at one point

Short term Fluctuation as an Individual Standard of Accuracy

It is obvious that a visual field examination should not only yield threshold results but should also provide a criterium for the reliability of these data The simplest standard of reliability is the much discussed short term fluctuation encountered in repeated threshold determinations at a fixed point of a

visual field (later averaged over several retinal points) where repetitions are carried out at the same session In order to determine the personal index of reliability with a minimum additional effort two threshold determinations should be carried out instead of single measurements for a limited number of points K in the visual field Below we will show that roughly for $K = 10$ of these double determinations the deviation σ can be fairly accurately estimated

Let s_k and s'_k be the first and the second result respectively at the retinal point k ($k = 1$ K) at the same session The sample estimate for σ is then

$$\sigma = \sqrt{K^{-1} \sum_{k} {}^{1}/_{2} \; (s_k - s'_k)^2} \qquad (9)$$

Naturally a sample estimate (9) based on a small number of double determinations K has only a limited reliability due to the stochastic character of s_k and s'_k In fact for a given standard deviation σ the estimate (i e the right hand side of (9)) has a probability of lying within $\sigma\left(1 \pm \sqrt{\frac{1}{2K}}\right)$ of 0 68

Therefore about $K = 10$ paired measurements will be necessary requiring an additional observation time of the order of one minute in order to yield σ with an accuracy of about ± 25 % which is sufficient to allow repartition into three reliability classes with a certain amount of safety We recall that σ ranged from *about 1 dB (stable observer) to about 4 dB (unreliable observer) in a sample* of 16 visual fields of untrained subjects

Note the assumption that σ is independent of retinal location is a simplification Due to local sensitivity defects and fixation instability the variation at these points may be larger than implied by the mean σ

Spatial Correlations

Finally we would like to indicate in which areas the present analysis of static perimetry should be extended and at the same time mention where improvements in measurement methods should be sought

Hitherto considerations (including the contents of I) referred essentially to a single point of the visual field The measurement of the threshold S (x) at one point x was isolated and not considered in relation to threshold determinations of neighbouring points (we deviated from this concept only in the

definition of the synchronous component L^f for long term fluctuations) However there is a statistical correlation between the thresholds S (x) and S (x + y) for two neighbouring points x and x + y respectively If S (x) has been determined information will also have been obtained about S (x + y) due to the probability that the two thresholds do not deviate very much from each other From information theoretical considerations it is clear that this type of previous knowledge must be used in order to design an optimal technique of measurements

The degree of spatial correlation determines in principle the spatial resolution (i e the number of points) with which a visual field must be examined The introduction of a suitable correlation function and an estimation of its order of magnitude therefore appears desirable We will introduce a function v(y) suitable to a quantitative description of the spatial correlation of a visual field This is perhaps not the most elegant of the several mathematically almost equivalent possibilities However in our opinion it is quite suitable for practical problems

We consider two points of the visual field at a distance 2 y (a few degrees) which are symbolized by x + y and x − y whose central point is x In a localized linear approximation of the threshold S as a function of location S (x) is the arithmetic mean of the neighbouring thresholds S (x + y) and S (x − y) In reality however S (x) is fairly irregular and the deviation V of the true value for the threshold S (x) from the arithmetic mean (taken as a function of x for constant y) will have more stochastic than systematic character For a given class of visual fields we are less interested in the behaviour of the stochastic function $V = V_y(x)$ defined by

$$S\,(x) = {}^1/_2\,[S_0(x-y) + S_0(x+y)] + V_y(x) \tag{10}$$

than by its root mean square value over the entire visual field for fixed y

$$v(y) = \langle V_y^2 \rangle^{1/2} \tag{11}$$

v(y) is obviously a measure for the mean local irregularities of a visual field. Since for the purpose of definition the true thresholds are used and not fortuitous results of single measurements these irregularities do not arise from random deviations of measurements but for normal visual fields from the natural fine structure of contrast sensitivity (as a function of retinal location) and for pathological visual fields from local defects Obviously v depends on y intuitively we expect that v tends to increase monotonically with an increasing y in particular it follows from (10) and (11) that v(0) = 0

In order to indicate an order of magnitude the correlation function v(y) as obtained from the analysis of three visual fields is stated although at the

moment these data are insufficient for any kind of further conclusions (A and B are normal visual fields C has dense local defects)

Visual field A	v(0) = 0	v(2) = 0 5	v(5) = 0 5	v(10) = 0 5 dB
Visual field B	v(0) = 0		v(5) = 0 7	v(10) = 0 7 dB
Visual field C	v(0) = 0		v(5) = 2 2	v(10) 3 5 dB

For the empirical determination of v(y) from (10) and (11) results of single threshold measurements (or the average of several measurements of the same threshold) will be substituted for the demanded values of the true thresholds S The effect on v(y) of the random deviation of the results of measurement must be eliminated by calculation

A further extension of the prevailing technique of point measurement which is in part associated to the subject of spatial correlation is conceivable as follows If thresholds are already known for a lattice of basic points the object of a refined spatial examination is not necessarily to determine as accurately as possible the thresholds for intermediate points In certain cases (early glaucomatous defects) it is sufficient to decide for the intermediate points whether the threshold is significantly inferior to an interpolated value This concept has already been considered (Fankhauser et al 1971 Koch et al 1971)

Finally the introduction of further quantities defined over the entire visual field must be considered as for example the mean square deviation of the threshold from a linear function of excentricity or the deviation from circular symmetry Frisen & Frisen (1975) have examined the hypothesis that normal isopters of the central visual field are elliptical with the exception of random deviations and they have applied statistical methods in order to detect small deviations from elliptical shape The advantage then lies as well in a reduction of data as in such quantities are little influenced by fortuitous single results However in this context there is the drawback that in forming summations over the entire visual field significant local deviations may be lost. In connexion with these quantities the aspects of measurement techniques alone are less interesting than the problem of the magnitude of the correlation between these quantities and the stages of certain pathological states

Zusammenfassung

Schwellenfluktuationen werden mithilfe statistischer Methoden in Kurzzeit und Langzeiteffekte zerlegt Die numerischen Werte der Kurzzeit Langzeit und Totalstreuung werden angegeben so wie sie sich aus der ausgedehnten Analyse von sechszehn gesunden und pathologischen Gesichtsfeldern ergeben haben Spezielle Beachtung verdienen

die zufälligen Aenderungen der Schwellenresultate gegenüber denjenigen einer früheren Gesichtsfelduntersuchung Schliesslich führen wir den Begriff der räumlichen Korrelationen in die statistische Analyse von Gesichtsfeldern ein

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ZUR AUTOMATISIERUNG DER PERIMETRIE

Darstellungsmethoden perimetrischer Untersuchungsergebnisse

VON

BEAT WEBER und JÜRG SPAHR

Die vorliegende Arbeit befasst sich mit Problemen der Darstellung perimetrischer Untersuchungsergebnisse und den Lösungsmöglichkeiten, die sich durch die Verwendung eines Computers und eines Datensichtgeräts ergeben. Besonderes Gewicht wurde auf dreidimensionale Darstellungen mit Berücksichtigung der Sichtbarkeit sowie auf zweidimensionale Isopterendarstellungen gelegt.

Key words: perimetry – visual field – automation – displays: three-dimensional – isopter – histogram.

Die heute gebräuchlichen Darstellungsmethoden von perimetrischen Untersuchungsdaten sind eng mit den angewendeten Untersuchungsmethoden verknüpft. So werden seit Jahrzehnten die mit der kinetischen Methode gewonnenen Lichtunterschiedsempfindlichkeiten (LUE) im Gesichtsfeld des Menschen in Form von Isopteren, Kurven gleicher Empfindlichkeit, dargestellt. Die Einführung der statischen Perimetrie brachte eine neue Darstellungsform. Sogenannte Profilschnitte werden entweder in meridionaler Richtung durch das Gesichtsfeld (Sloan 1939, Harms 1940), in konzentrischen Kreisen um das Gesichtsfeldzentrum (Ourgaud und Mitarb. 1961) oder in beliebigen Richtungen (Fankhauser und Mitarb. 1966) gelegt.

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Durch die Automatisierung der Perimetrie mit Hilfe eines Computers (Spahr 1973) trat nebst vielen anderen neuen Aspekten auch das Problem der Datenverarbeitung und insbesondere das der Darstellung der Resultate auf Obwohl der Computer primar zur Durchfuhrung von Untersuchungen d h zur Steuerung des Perimeters vorgesehen ist kann er naturlich auch zur Verarbeitung und – mit den entsprechenden Peripheriegeraten ausgerustet – zur Speicherung und zur Darstellung von Untersuchungsdaten eingesetzt werden Dank den heute erhaltlichen Datensichtgeraten (Wir benutzen zur Zeit ein Datensichtgerat (4010) und ein Kopiergerat (4610) der Firma Tektronix) die zusatzlich zur alphanumerischen auch noch eine graphische Ausgabe erlauben hat man grossen Spielraum in der Programmierung von Darstellungsarten So ist beispielsweise eine Isopterendarstellung auch fur statisch gewonnene Untersuchungsresultate moglich und umgekehrt konnen die Daten einer kinetischen Messung auch in Form von Schnitten durch das Gesichtsfeld dargestellt werden Dabei bleibt das Hauptanliegen perimetrischer Darstellungsmethoden darin bestehen die Untersuchungsergebnisse moglichst ubersichtlich einpragsam und ohne Informationsverluste darzustellen

Problemstellung

Die Lichtunterschiedsempfindlichkeit (LUE) ist unter bestimmten Bedingungen am Fixationspunkt am grossten und nimmt gegen die Peripherie hin ab Der Wertevorrat der gesamten Lichtempfindlichkeitsfunktion kann bis zu 12 Zehnerpotenzen umfassen der Bereich der bei der klinischen Perimetrie getestet wird betragt ungefahr 5 Zehnerpotenzen und wird im allgemeinen logarithmisch dargestellt (z B Dezibelskala wobei 1 Dezibel (dB) gleich 0 1 log Einheiten entspricht)

Wird die Empfindlichkeit als Funktion der Gesichtsfeldkoordinaten aufgetragen so erhalt man ein Empfindlichkeitsgebirge dessen Gestalt stark von der Adaptationsleuchtdichte des Umfeldes abhangig ist

Es stellt sich also das Problem dieses dreidimensionale Empfindlichkeitsgebirge in die zweidimensionale Zeichnungsebene abzubilden Dabei sollen die Darstellungsmethoden den raumlichen Charakter der LUE berucksichtigen und ausserdem folgende Eigenschaften aufweisen

1 Uebersichtlich und einpragsam Der Augenarzt soll die Untersuchungsdaten mit einem Blick erfassen und sich ein qualitatives Bild des vorliegenden Gesichtsfeldes oder von Teilen desselben verschaffen konnen

2 *Genau und zuverlassig* Die einem Messpunkt zugeordnete LUE muss auch quantitativ (Zahlenangabe Massstab) jederzeit leicht zuganglich sein Fehlende Messdaten dürfen nicht durch fragwurdige Interpolationsverfahren erganzt werden um damit die Darstellung verschonern zu konnen.

3 *Umfassend und spezifisch* Die Untersuchungsdaten mussen ohne Zeitverlust sowohl in ihrer Gesamtheit (Totalinformation) als auch in ausgewahlten Teilen (Teilinformation) dargestellt werden konnen

4 *Schnell realisierbar* Graphische Darstellungen als Mittel zur Interpretation von perimetrischen Untersuchungsergebnissen mussen schnell und problemlos realisiert werden konnen damit sie dem Arzt eine wirkliche Hilfe bedeuten Zeitraubende mathematische Berechnungen von komplexen Darstellungen konnen von einem Computer aber ohne weiteres unbeaufsichtigt (z B uber Nacht) gemacht und die Daten in leicht zuganglicher Weise (z B auf Magnetband) gespeichert werden

Das Ziel dieser Arbeit besteht darin neuartige Darstellungsmethoden aufzuzeigen die einerseits die erwahnten Eigenschaften erfullen und anderseits die Vorteile der herkommlichen Isopteren wie auch der Profildarstellung in sich vereinigen sollen

Losungsvorschlage

Um verschiedene Darstellungsmethoden an einem moglichst breiten Spektrum in der Praxis auftretender Gesichtsfelder vorzustellen wurden die Daten eines Gesunden und eines Glaukompatienten verwendet Dabei wurde die LUE Verteilung (L) in kartesischen Koordinaten auf einem quadratischen Netz von 11 x 11 Punkten gemessen

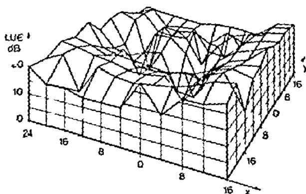
$$L = L(m\ n) \quad m = -24 \quad -20^{\circ} \quad 0^{\circ} \quad 16$$
$$n = -24^{\circ} \quad -20^{\circ} \quad 0^{\circ} \quad 16^{\circ}$$

a) Perspektivische dreidimensionale Darstellung mit Berücksichtigung der Sichtbarkeit

Erste Versuche zur Darstellung von perimetrischen Untersuchungsresultaten in Form von dreidimensionalen Graphiken wurden in fruheren Arbeiten (Spahr 1973 Spahr und Mitarb 1974) beschrieben Dabei wurde die einfachste projektive Darstellung der LUE Funktion angewendet Man erhalt diese durch Parallel bzw durch perspektivische Projektion der Polygonzuge

L_m (n) = L (m n) fur konstantes m

L_n (m) = L (m n) fur konstantes n



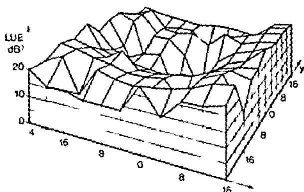


Abb 1

Dreidimensionale Darstellung des Gesichtsfeldes eines Patienten mit multiplen relativen parazentralen Skotomata Oben ohne Berucksichtigung Unten mit Berucksichtigung der Sichtbarkeit

Diese sehr einfach zu programmierende Darstellungsmethode hat leider den grossen Nachteil dass die Anschaulichkeit und die Uebersichtlichkeit infolge Ueberschneidungen bei komplexen Verhaltnissen sehr leicht verloren gehen (vgl Abb 1 oben) Es ist deshalb naheliegend eine dreidimensionale Darstellung der LUE zu entwickeln bei der die Sichtbarkeit berucksichtigt wird d h die LUE Verteilung ist als undurchsichtige Flache aufzufassen von der nur diejenigen Teile gezeichnet werden die vom jeweiligen Betrachterstandort direkt gesehen werden konnen (vgl Abb 1 unten) In einem Anhang (A) wird

eine mathematische Methode erlautert die eine Programmierung dieser speziellen Darstellungsmethode erlaubt

Um Informationsverluste zu vermeiden die dadurch entstehen konnen dass gewisse Teile des Empfindlichkeitsgebirges durch weiter vorne liegende verdeckt werden muss die Moglichkeit zur Variation des Betrachterstandortes geschaffen werden In Abb 2 wurde ein einziges Gesichtsfeld viermal dargestellt wobei die Betrachtungsrichtung jeweils um 90° gedreht wurde. Um extreme Empfindlichkeitssenken besser sichtbar zu machen wurde hier zusatzlich eine Inversion der Empfindlichkeiten vorgenommen d h Senken wurden als Hugel gezeichnet und umgekehrt (L → L –L)

b) Dreidimensionale Histogramm – Darstellung

Die Darstellung der LUE Verteilung als dreidimensionales Histogramm stellt einen weiteren Versuch dar dem Raumempfinden des Menschen entgegenzukommen Ausserdem spiegelt dieses Diagramm den wahren Informationsgehalt

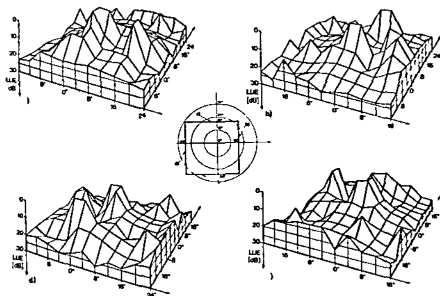


Abb 2

Dreidimensionale Darstellung des gleichen Gesichtsfeldes wie in Abb 1 Die LUE Werte wurden hier invertiert um Empfindlichkeitssenken hervorzuheben. Das Gesichtsfeld wurde aus vier verschiedenen Blickrichtungen (a, b c d siehe Schema im Zentrum) aufgezeichnet

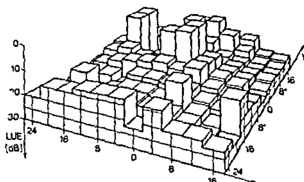


Abb 3
Dreidimensionale Histogramm – Darstellung des gleichen Gesichtsfeldes wie in Abb 1 (mit Inversion)

der Messung wieder indem jedem effektiv gemessenen Punkt ein Quader proportionaler Hohe entspricht Auch hier besteht naturlich wieder die Moglichkeit zur Inversion der Empfindlichkeiten In Abb 3 wurde davon Gebrauch gemacht und es ist sehr leicht zu sehen dass diese Abbildung das gleiche Gesichtsfeld wie Abb 2 a) darstellt

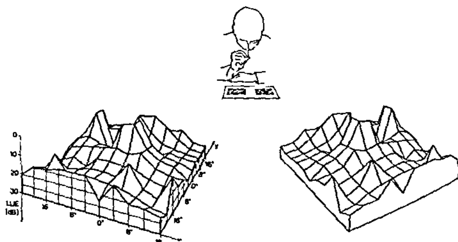
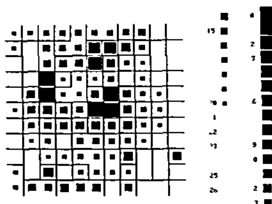


Abb 4
Disparates Stereopaar des gleichen Gesichtsfeldes wie in Abb 1 (mit Inversion) Die stereoskopische Betrachtung erfolgt mit Hilfe eines Spiegels von ca 10 cm Durchmesser in einer Distanz von ca 20 cm Wie in der Skizze angedeutet wird die Figur links mit dem linken Auge direkt und die Figur rechts mit dem rechten Auge so uber den Spiegel betrachtet dass beide Bilder zur Deckung gebracht werden

c) Stereoskopische Betrachtung perspektivischer Darstellungen

Bekanntlich entsteht bei stereoskopischer Betrachtung von disparaten Paaren im Gehirn der Eindruck eines dreidimensionalen plastischen Bildes Mit Hilfe eines Computers lassen sich ohne weiteres solche Stereopaare berechnen In Abb 4 wurde das gleiche Gesichtsfeld wie in den vorausgehenden Abbildungen fur eine stereoskopische Betrachtung aufgezeichnet Naturlich lasst sich die Querdisparation und damit der Eindruck der Raumtiefe im Computerprogramm fast beliebig variieren In Abb 4 wurde ein Augenabstand von 6 cm und eine Objektdistanz von 30 cm vorausgesetzt

Der Nachteil der stereoskopischen Betrachtung besteht darin dass man nicht ohne Hilfsmittel (Stereoskop Spiegel) auskommt



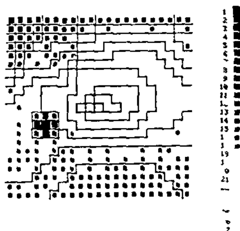
21	15	18	17	16	17	17	16	15	22	23
20	23	13	16	16	6	5	11	18	23	24
22	23	15	14	1	3	13	19	21	23	2
25	-2	0	21	-0	2	17	23	20	22	23
24	13	0	20	20	1		1	19	2	2
		12	15	6		0	13	0	20	26
2	7	5			12		2	9	21	22
23	2	19	-2	6		17	8	2	23	2
2	23	2	20	10		9		22	25	3
-0	23	0	2		10	9	-0	2	25	26
20	15		3			3		2		23

Abb 5

Gleiches Gesichtsfeld wie in Abb 1 Oben Flachen proportional zur Empfindlichkeit (vgl dB Skala) Unten Empfindlichkeitswerte in Form einer Zahlentafel

d) Darstellung durch proportionale Flächen

Falls man die perimetrierten Werte auch quantitativ aus einer Graphik herauslesen möchte, so braucht man einen Massstab, der eine eindeutige Zuordnung erlaubt. Besser geeignet als eine dreidimensionale Darstellung ist in diesem Fall eine zweidimensionale Graphik, in der die dritte Komponente beispielsweise durch eine zu ihr proportionale Fläche dargestellt wird. In Abb. 5 (oben) wurde jedem Messwert ein Quadrat zugeordnet, wobei die Grösse eines Quadrates gerade *proportional* zur gemessenen Empfindlichkeit L bzw. zu L_{max} – L ist.



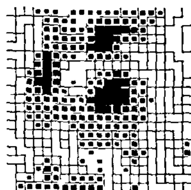


Abb. 6
Beispiele eines gesunden (oben) und eines pathologischen (unten) Gesichtsfeldes nach einmaliger Interpolation der Empfindlichkeitswerte (vgl. dB-Skala)

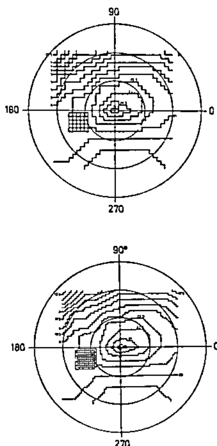


Abb 7
Beispiele eines gesunden Gesichtsfeldes nach zweifacher (oben) und nach vierfacher (unten) Interpolation der Empfindlichkeitswerte

Diese Darstellungsformen von Flachen variabler Grosse bzw von verschiedenen Helligkeitswerten auf Flachen sind weit verbreitet denn sie sind leicht kon struierbar und sichern eine gute Lesbarkeit (Bertin 1974) In Verbindung mit einer Legende oder mit einer entsprechenden Zahlentafel (Abb 5 unten) sind die quantitativen Werte fur jeden Messpunkt leicht zuganglich

Durch lineare Interpolation (vgl Anhang (B)) kann das Darstellungsraster verfeinert und die Uebersichtlichkeit verbessert werden (Abb 6 oben und unten) zusatzliche Information gewinnt man damit aber nicht

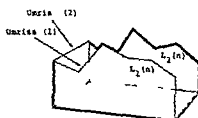
Dankvermerk

Die Autoren danken den Herren Professoren F Fankhauser und H Bebie fur ihre kritischen Hinweise und Kommentare die diese Arbeit sehr gefordert haben

Mathematischer Anhang

(A) Zur Programmierung einer dreidimensionalen Darstellung mit Berücksichtigung der Sichtbarkeit

Ein dreidimensionales Bild kann aus den geschlossenen Polygonzugen $L_m(n)$ wie folgt aufgebaut werden (vgl Skizze (a))



Zuerst wird der vorderste Polygonzug ($L_1(n)$) gezeichnet Dieser ist vollstandig sichtbar und bildet gerade den ersten Umriss

Fur jeden Punkt jedes folgenden Polygonzuges ($L_m(n)$ $m = 2$ M) muss entschieden werden ob er innerhalb (nicht sichtbar) oder ausserhalb (sichtbar) des bestehenden Umrisses liegt Falls ein Punkt sichtbar ist so wird er gezeichnet und in den neuen Umriss eingefugt.

Der Test ob ein Punkt innerhalb oder ausserhalb eines bestehenden Umrisses liegt, ist der Kern der Programmierung dieser speziellen Darstellungsart und soll deshalb kurz in seiner mathematischen Form erlautert werden

Voraussetzungen

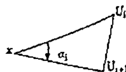
U_i (Umrisspunkte $i = 1$ 2 I) sei ein geschlossener ebener Polygonzug und x sei ein Punkt in derselben Ebene

Fur die folgende mathematische Ableitung ist es zweckmassig U_i und x durch *komplexe Zahlen darzustellen*

$n(x\ U_i)$ sei die Umlaufszahl von x bezuglich U_i

$$\text{Dann gilt}\quad n(x\ U_i) = \frac{1}{2\pi} \sum_{i=1}^{I} \alpha_i$$

$$\text{mit}\quad \alpha_i = \arg \frac{U_{i+1} - x}{U_i - x}$$

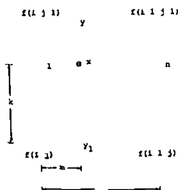


Also $n(x\,U_i) = \frac{1}{2\pi} \sum_{i=1}^{I} \arg \frac{U_{i+1}-x}{U_i-x}$ (wobei $U_{I+1} = U_1$)

Es gilt $n(x\,U_i) = \begin{cases} 0 \longrightarrow U_i \text{ umschliesst } x \text{ nicht} \\ k \longrightarrow U_i \text{ umlauft } x\ k \text{ mal} \end{cases}$

(B) Zur linearen Interpolation einer über einem quadratischen Netz definierten Funktion f (i j)

Fur die in Skizze (b) gezeichneten Eckpunkte ( ) konnen durch folgende lineare Interpolationen sehr leicht Zwischenwerte berechnet werden



Zuerst wird die Funktion an der Stelle x_1 bestimmt

$$x_1 = f(i\,j) + \frac{k\,l}{n\,l}\,[f(i\,j+1) - f(i\,j)]$$

$$= \frac{1}{n\,l}\,[(n\ k)\ f(i\,j) + (k\ l)\ f(i\,j+1)]$$

Analog gilt fur die Funktion an der Stelle x_n

$$x_n = \frac{1}{n\,l}\,[(n\ k)\ f(i+1\,j) + (k\ l)\ f(i+1\,j+1)]$$

Aus x_1 und x kann der Wert der Funktion an der Stelle x gemass folgender Formel berechnet werden

$$x = \frac{1}{n\,l}\,[(n\ m)\ x_1 + (m\ l)\ x_n]$$

und damit

$$x = \frac{1}{(n\ 1)} \{(n\ m)\ (n\ k)\ f(i\ j) + (n\ m)\ (k\ 1)\ f(i\ j+1)$$

$$+ (m\ 1)\ (n\ k)\ f(i+1\ j) + (m\ 1)\ (k\ 1)\ f(i+1\ j+1)\}$$

Anmerkung Wie leicht gezeigt werden kann fuhrt eine Interpolation uber y_1 und y_n zum gleichen Resultat

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MAST CELLS AND PTERYGIUM

BY

K. S RATNAKAR V GOSWAMY and L P AGARWAL

A total of thirty pterygia were studied for mast cells using metachromatic dye (toluidine blue) together with routine histological stains. On microscopic examination the lesion was differentiated and classified into angiomatous, fibrous and mixed varieties based on the vascular and collagenous components The mast cell counts were undertaken in all types and were found to have significant correlation with the morphological types when compared to normal conjunctiva. 15.1 ± 3.1 22.7 ± 3.8 9.5 ± 3.2 mast cells per mm were found in the angiomatous mixed and fibrous types respectively In the control material the mast cell count was 12.4 ± 2.3 per mm The results are discussed. It is believed that mast cells are actively involved in the genesis and progress of pterygium.

Key words pterygium – conjunctival mast cells – histological types of pterygium.

Pterygium is a common kerato conjunctival lesion encountered in the tropics Despite several clinical and epidemiological studies the pathogenesis of pterygium remains obscure Heredity and environmental factors such as exposure

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Table I
Distribution of mast cells in the pterygia of various morphological types

Types	No of cases	Mast cells (per mm² area)
		(Mean ± standard deviation)
Angiomatous	12	15 1 ± 3 1
Fibrous	6	9 5 ± 3 2
Mixed	12	22 7 ± 3 8
Control	16	12 4 ± 2 3

to a sunny dry atmosphere have been incriminated in the genesis of the disease (Forsius & Eriksson 1962) Clinical and pathological aspects of the lesion have been fully described by several authors (Fuchs 1892 Hilgers 1960) Mast cells are known to be associated with allergic and fibroblastic diseases (Fernex 1968) However the mast cells in pterygium have not received much attention hitherto It is therefore considered worthwhile to investigate this problem

Materials and Methods

A total of thirty pterygia received in the past few years from the hospital of this centre were used for the study The tissues were fixed in 10 per cent formalin and processed for paraffin embedding Several sections were cut at 5 micron intervals and stained by 1 per cent aqueous toluidine blue buffered to pH 3 The mast cells were counted using a calibrated binocular microscope. The number of mast cells were expressed per mm² Conjunctival tissues from autopsy cases with no ocular diseases were similarly studied and used as control material

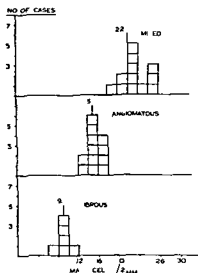


Fig 1
Distribution of mast cells in the three histological types of pterygium The figures over the bars indicate the average number of mast cells in each type

Results

The pterygia were histologically divided into three morphological types angiomatous fibrous and mixed (Ratnakar 1976) The basis for this division is as follows

Angiomatous The stroma contains a significant number of vascular channels with oedema in the intervascular space

Fibrous The stroma is predominantly fibrous with a few scattered vascular elements

Mixed The stroma contains both vascular channels and collagenous tissue in equal proportions the latter is often in thin bundles

The mast cell distribution in the three types is shown in Table I The highest number of mast cells was 22 7 ± 3 8 per mm (mean ± standard deviation) This was found in the mixed type of pterygia as compared with the controls and the other types The angiomatous type showed a mean mast cell count of 15 1 ± 3 1 mm² The fibrous type contained the least number of 9 5 ± 3 2 mast cells per mm² The control contained an average of 12 4 mast cells per mm of tissue section The results are shown graphically in Fig 1

Comments

Pterygium is of paramount clinical importance due to its characteristic involvement of the cornea and its capacity to progress beyond the central region The mechanism underlying its genesis and progress are incompletely understood A *dominant hereditary pattern* an association with *exposure to actinic rays* a histological and clinical resemblance to a neoplastic process accompanying multiple dietary deficiency factors (Beard & Dimitry 1945) have all been considered to be involved either directly or indirectly in the evolution of pterygium

Mast cells are widely distributed connective tissue cells which contain multiple biologically active substances such as heparin histamine and 5 HT in their metachromatic granules The degranulation with the release of these substances into the tissues occurs in response to a variety of stimuli (Leblanc 1963 Uvnas 1964) Several environmental and endocrinological factors have been found to affect the mast cell system in the body Mast cell secretion and their multiplication are intimately associated processes (Roth et al 1963) The increase in mast cell count hyperplasia in any particular area is therefore an indicator of constant mast cell stimulation with degranulation in that zone In the present investigation it is shown that pterygia contain an increased number of mast cells as compared with the controls with the exception of the fibrous type

In the absence of any obvious infection or infestation the principal factors that may be considered as being responsible for the local increase of mast cells are chronic *exposure to ultraviolet rays* (Valtonen & Kock 1963) and local allergy Valtonen (1961) reported an increased number of mast cells in the skin of mice exposed to ultraviolet rays

It has been postulated that trephocytosis which is a controlling process in the organization of connective tissue is one of the most important functions subserved by mast cells (Riley 1963 Dougherty & Dolowitz 1964) Pathological changes comparable to scleroderma dermatomyositis myelosclerosis etc have been reproduced in experimental animals based on this assumption (Selye 1962 1963) Histamine liberated on degranulation results in vasodilatation and increased permeability The oedema fluid contains a protein rich exudate which may itself act as a fibrogenic stimulant FioreDonati & Miltke (1960) consider serotonin more important than histamine in fibroplasia Furthermore heparin has been shown to augment maturation of collagen fibres and the *in vitro polymerization of soluble collagen (Morrione 1952) In addition* Holczinger & Devenyi (1955) believe that heparin acts as an inhibitor of hyaluronidase

The early phase of all fibroplastic lesions in experimental models is essentially a vascular proliferation and oedema The angiomatous histological type described in this investigation possibly represents this stage Waldenstrom (1967)

reported that an increased number of mast cells in the bone marrow is followed by fibrous alteration of the red marrow Several fibroplastic lesions such as endocardial fibrosis and scleroderma are also considered to be a manifestation of mast cell activity (McDonald & Robbins 1957 Smith 1958) Similarly hepatic cirrhosis could not be produced in rats containing a reduced number of mast cells (Ahlquist 1960) Based on these facts it can logically be inferred that the fibrous type of pterygium represents an end stage whereas the mixed type with an increased number of mast cells represents an intermediary stage

Acknowledgment

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INTERFERENCE FILTER FOR COLOUR AND BLACK AND WHITE FLUORESCEIN ANGIOGRAPHY

BY

B KORNACKI P ALGVERE and T STEFANIAK

A new dichromic interference filter was used as the excitation filter in colour and black and white fluorescein angiography of the human fundus The interference filter transmits light shorter than 490 nm (blue) and longer than 640 nm (red) In colour photography the red light shows the topography of the fundus
In black and white photography the red light is prevented from reaching the fundus by an additional absorption filter used together with the interference filter These two comprise the excitation filter which eliminates the pseudo fluorescence from black and white angiograms

Key words fluorescein angiography – colour – black and white – interference filter – human eye

A camera used for fluorescein angiography of the fundus must be equipped with two filters (*i*) *an excitation filter placed in the path of the light beam* produced by the flash lamp (ii) a barrier filter placed in front of the film An ideal excitation filter should ensure the maximal transmission of light in the spectral band absorbed by the fluorescein (460–480 nm) A perfect barrier filter should fully transmit the light emitted from the fluorescent dye the wavelength of which is around 525 nm The barrier filter must have a total or almost total absorption of light of other wavelengths including that which is transmitted by the excitation filter In addition the barrier filter should cut off the light reflected from the undyed structures of the fundus

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The filters most frequently used in fluorescein angiography of the fundus are absorption filters of gelatin or glass (Ferrer 1971) These include sets of Kodak Wratten filters such as KW 47A and KW 15 (Allen et al 1966 Ferrer 1968) KW 47A and Schott GG 14 (Wessing 1967) and Fuji FG 18 and FG 12 (Shikano & Shimizu 1968) One drawback of the absorption type of excitation filters is that at a relatively good transmittance of the desired wavelength they transmit a considerable amount of light (2–10 %) of longer wevelengths This light is not absorbed by the barrier filter and may affect the film a phenomenon known as pseudo fluorescence (see Machemer et al 1970)

Interference filters represent a much more efficient type of colour filter since they show a high energy transmission at peak levels and a sharp cut off with respect to other wavelengths The use of narrow band interference filters (Baird Atomic B 4) in fluorescein angiography has previously been reported (Hodge Clemett 1966 Haining & Lancaster 1968)

Evidence favouring wide band filters for fluorescein angiography has also been presented (Allen & Frazer 1971)

The present paper describes a new broad band interference filter used as an excitation filter in black and white as well as in colour fluorescein angiography

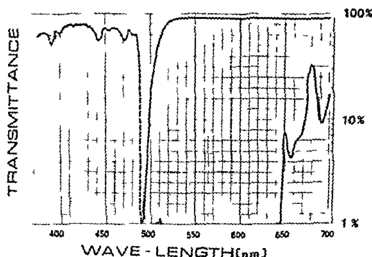


Fig 1

Light transmittance (in logarithmic scale) plotted against wavelength for filters used in *colour* fluorescein angiography The dichromic interference filter (dashed line) transmits blue light shorter than 490 nm and some red light in the range of 650–700 nm The barrier filter (continuous line) has a high transmittance at 515 nm (the fluorescence emission) and continuing at longer wavelengths

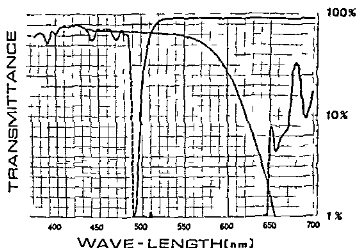


Fig 2

Light transmittance (in logarithmic scale) plotted against wavelength for filters used in *black and white* fluorescein angiography The excitation filter consists of the di chromic interference filter (dashed line) and a glass filter (dotted line) that absorbs the red light (about 650 nm and longer wavelengths) The barrier filter (continuous line) is the same one shown in Fig 1

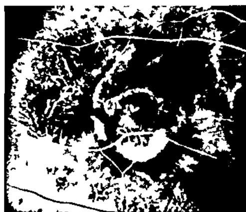
Methods

A dichromic interference filter (COBRABID Warsaw Poland) was used as the excitation filter in the photography of fluorescein angiography The interference filter transmits light of the following wavelengths about 400–490 nm (blue) and 640–700 nm (red) There is a very sharp cut off at 490 nm (Fig 1) An absorption filter of glass (Schott GG 14–3) was used as the barrier filter it has a high transmission beginning at 500 nm and continuing at longer wave lengths *This combination of filters is useful in the colour photography of fluo rescein angiography* The excitation light contains a considerable amount of red light which is very well reflected from the fundus and transmitted through the barrier filter In this way the reddish colour and the topography of the fundus can be recorded on colour films

In *black and white* photography the red light causes pseudo fluorescence and should therefore be eliminated Accordingly an absorption glass filter (Schott BG 18–2) was placed in the path of the excitation light beam in addition to the interference filter These two filters formed the excitation filter

The absorption filter cuts off the red light (Fig 2) However some wave lengths around 650 nm may be transmitted to the fundus The intensity of the


5A


5B


5C

Fig 5

Fluorescein angiograms from the fundus of a 28 year old man with old choroiditic scars in the macular area A 10 sec B 15 sec C 30 sec after injection of fluorescein into an antecubital vein In the atrophic macular scar there are newly formed sub retinal vessels that seem to be supplied by the choroidal circulation Above the macula, there are large pigmented areas not easily recognized in black and white photographs *Cf* colour angiograms (Fig 6)







Fig 6

Fluorescein angiograms from the eye described in Fig 5 A 10 sec B 20 sec. and C 3 min after fluorescein injection The topography of the fundus is clearly visible. The pigmented area above the macula is easily recognized and the vessel free para macular areas are distinguishable. The fluorescent dye displays a yellow hue when viewed against a reddish background but appears closer to green against a black (pigmented) background

the fundus such as the optic disc are not visible unless dyed with fluorescein Under such conditions there can be no confusion as to what is dyed and what is not dyed with fluorescein (Fig 5)

Fluorescein angiograms in colour depict the details of the fundus as well as the flow of the fluorescent dye If visible pathological changes are present (such as exudates hemorrhages gliosis or fibrosis) they are seen superimposed on the fluorescein pattern The distribution of the dye can be analyzed in relation to the topography of the fundus pathology A colour photograph of the fundus providing a detailed backcloth for the fluorescein distribution, facilitates the interpretation of the angiograms Examples of angiograms in colour are shown in Fig 6 they can be compared with black and white angiograms from the same eye (Fig 5)

Discussion

The dichromic interference filter used meets all the requirements for an excitation filter in fluorescein angiography The filter ensures excellent transmittance of light in the desired blue part of the spectrum It has a sharp cut off at about 490 nm However it does transmit some red light in the 640–700 nm range In the black and white photography of fluorescein angiograms the excitation filter must be combined with a glass filter that absorbs the red light When the excitation light passes through these two filters practically no light of wavelengths longer than 490 nm reaches the fundus When combined with a barrier filter only light emitted from the fluorescent dye will reach the film This method provides high contrast pictures eliminating entirely the phenomenon of pseudo fluorescence i e the blackening of film by light reflected from the undyed structures

Elimination of the pseudo fluorescence however is combined with a reduction of information on the fundus topography making orientation more difficult When the fundus is photographed in colour the picture generally contains considerably more information than a black and white photograph Colour photography of the fluorescein angiograms depicts the details of the fundus in an almost natural hue This fact facilitates the interpretation of fluorescein changes since they can be easily related to fundus topography

Fluorescein angiograms in colour have been published earlier (Shikano & Shimizu 1968 Matsui 1971 Hendrickson et al 1970 Schatz et al 1973 Grounauer & Faggioni 1975)

The colour technique affords several advantages over black and white photography but generally does not seem to have the excellent contrast and resolving power exhibited by black and white pictures

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TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY 1975

EDITED BY

GUNNAR LENNERSTRAND

Meeting in Västerås April 12 1975
Symposium on Surgery of Retinal Detachment

B Rosengren & S Österlin *Model experiments illustrating hydrodynamic events in the vitreous space and their significance for retinal detachment*

The exact mechanisms for retinal detachment in the presence of a retinal tear are not known Sometimes immobilization of the eye reduces the elevation of the retina and when the eye is allowed to move freely the detachment increases It could be that fluid currents in the vitreous are responsible for the retinal re detachment in these cases This idea has been tested in the following model experiments

A glass container somewhat larger than the eye was filled with water in which lipid particles were suspended Displacement of the fluid was visible in the optical section obtained by a slit lamp During quick rotatory movements resembling saccadic eye movements in speed and magnitude marked displacements of the fluid were seen confined to the periphery of the container We have studied the influence of these peripheral currents on a circular latex membrane (0 1 mm thick and 45 mm in diameter) attached to the inner wall of the container If the membrane had a central hole, rotatory movements caused an elevation of the membrane away from the wall of the container in much the same way as the retina is separated from the wall of the eye in retinal detachment

Discussion

B Rosengren The question was raised as to whether model experiments of this kind have any clinical applicability In my opinion they suggest that fixation of the globe may reduce an elevation of the retina in retinal detachment

B Linder *Scleral buckling after Custodis – indication and technique*

Scleral buckling with polyviol after diathermy treatment was introduced some 25 years ago by Custodis He described excellent results Polyviol was however not well tolerated and some serious complications were reported Lincoff replaced polyviol with silicone and diathermy with cryo treatment The rate of complications diminished and the method was then used the world over

About 70 % of all detachments can be treated with the episcleral plomb Detachments without any hole in aphakic patients with giant ruptures and preretinal vitreous tractions and detachments with several holes in retinal degenerations are not suitable for treatment by this method

The most important part of the technique is an exact positioning of the buckle over the hole The plomb may be placed radially or parallel to the limbus

The main complications occur during drainage of the subretinal fluid or as a result of it Therefore drainage should be avoided in most cases

S Österlin *Scleral buckling with a circling element – Indications and surgical technique*

P Syrdalen *Removal of encircling band (cerclage) as treatment for some post operative complications after retinal detachment surgery*

Over a 10 year period from 1965–1974 990 encircling procedures were performed for retinal detachment (silicone band and tantalum clip) In the same period 43 cerclages were removed (4.3 % of the total number of eyes treated) The causes for the removal were pain (63 %) chronic irritable eye (51 %) conjunctival fistula (44 %) tight cerclage (21 %) haemorrhage in the cerclage bed usually on the place where the clip was situated (12 %) cerclage too far behind or anterior to the equator (9 %) glaucoma (4 %) and endophthalmitis (2 %)

Retina was attached in 22 eyes before and after removal of the cerclage Redetachment occurred in one eye which then was treated with a new cerclage resulting in reattachment of the retina In the remaining 21 eyes the retina was detached and further retinal detachment surgery was not indicated Removal of the cerclage was performed in order to free the patient from pain or a chronic irritable eye

The average time from retinal detachment surgery to removal of the cerclage was one year and five months (minimum 11 days and maximum 10 years) In 37 eyes the cerclage was removed more than 30 days after retinal detachment surgery Mechanical factors are considered to be the causes of complications which occur that late in the postoperative course

In eyes treated with encircling silicone band the postoperative course may be complicated with pain and a chronic irritable eye and a conjunctival fistula may occur In such cases the removal of the encircling element can be an effective treatment There is little danger of redetachment if removal is performed more than 30 days after retinal detachment surgery The complications leading to the removal can be reduced by careful suture of the conjunctiva and Tenon s capsule and by correct tightening and positioning of the encircling element

P Algvere *Drainage of subretinal fluid in retinal detachment surgery*

A detachment of the retina is always associated with subretinal fluid between the neuro retina and pigment epithelium layer

If the retinal break cannot be sealed during the operation drainage of subretinal

fluid must be considered The drainage facilitates reattachment of the retina in many ways e g by reducing the pressure in the subretinal space and releasing most of the fluid interposed between the neuro retina and pigment epithelium A higher scleral buckle is formed which will reduce the intraocular volume relaxing the vitreous traction Even fairly rigid retinal folds might reattach

Drainage of subretinal fluid is necessary in eyes where a high elevation persists between an open retinal break and pigment epithelium

The release of fluid must be carried out where the detachment is highest and where large amounts of subretinal fluid are present This could be checked by ophthalmoscopy prior to the drainage because the fluid may easily shift to new areas during the operation The drainage should be carried out far from the retinal break especially if a large break is found to avoid a vitreous prolapse through the puncture The area immediately above the macula is dangerous since a subretinal bleeding if produced there would easily affect the macular function One should avoid the vortex veins and their tributaries and the long ciliary arteries and nerves In most cases the site of puncture will be a compromise

Drainage anterior to or under a scleral implant is usually safer than a puncture posterior to the buckle On the other hand the latter procedure is more effective in releasing the fluid and will result in a faster reattachment of the central retinal areas

A safe technique for draining the subretinal fluid consists of a sclerotomy (2-3 cm long) with a preplaced suture (e g 6-0 silk) so that the sclera is exposed By a trans pupillar focusing of light the area of the sclerotomy can be examined and large vessels recognized By a cautious diathermy of the choroid (low intensity long duration) a haemorrhage is prevented The exposed and protruding choroid is punctured in tangential direction By applying light pressure on the sclera over the retinal detach ment the subretinal fluid can be almost completely released Following this procedure the retina will immediately reattach provided that the vitreous traction is negligible

An adequate drainage of subretinal fluid is always advantageous and might im prove the prognosis The retina reattaches rapidly sometimes even on the operation table The duration of the detachment is shortened which facilitates the recovery of the function of the retinal receptor cells The postoperative care at the hospital is minimized

R Tornquist *Post equatorial retinal holes and their treatment*

Retinal holes behind the equator are usually caused by vitreous or retinal traction A local atrophy and an increased fragility of retina can be contributing factors Areas of lattice degeneration are sometimes found behind the equator close to retinal vessels Thus they are more radially orientated and holes are typically found at the ends or the margins Holes in area Martegiani are seen in high myopia with peripapillar atrophy An epipapillary membrane is an almost constant finding in these cases

In periphlebitis vascular occlusion and diabetic retinopathy a shrinkage in a part of retina can produce small holes usually near retinal vessels The origin of macular holes is obscure and the diagnosis always very difficult In perforating injuries big tears are sometimes caused by shrinking retinal tissue

Light coagulation is generally the best method of achieving an adhesive retino choroiditis around holes in the posterior part of the eye Different buckling procedures are used but near the posterior pole (macular or parapapillar holes) the silver clip according to Kloti or the semi cerclage method of Liesenhoff are recommended

Meeting in Stockholm November 28 1975
Symposium on Diagnosis of Orbital Tumours

Moderator *B Tengroth*

Participants *T Bertelsen G Lloyd K Bergstrom S Cronqvist O Pallin E Kock E Schyberg*

S Cronqvist *Roentgen diagnosis*

Roentgen examinations of immediate interest are plain X ray of the orbital region, phlebography and angiography The last mentioned should not only include examination of the internal carotid artery but also of the external or even better super selective examination of the maxillary artery Isotope examination is in the majority of cases of no or only slight value

Plain X ray In cases with unilateral exophthalmus abnormal bone changes are to be expected in about 50–60 % Of the utmost diagnostic value is tomography with hypercycloid movement in frontal as well as in lateral projections

Orbital phlebography Orbital veins can be demonstrated after puncture of a frontal vein or after injection of contrast via a catheter introduced into the jugular vein. The first mentioned technique is to be preferred using a venous inflow catheter with an outer diameter of 1 2 or 1 4 mm Of importance is compression of the angular vein in connection with the injection of contrast Knowledge of the normal venous anatomy and its variations increases the diagnostic safety (ref Brismar Orbital phlebography I–IV *Acta Radiol Diag 15* (1974) 369 481 577 *16* (1975) 1)

Angiography An orbital tumour cause changes in caliber or dislocation of vessels and abnormal vessels or contrast blush may be seen It is important to consider the fact that the lateral and lower part of the orbit is fed from the maxillary artery and from the middle meningeal artery making selective angiography of those vessels or of the external carotid artery imperative for an adequate mapping

General Session

S Blomdahl & B Calissendorff *Ocular complications in renal transplant recipients*

50 renal transplant recipients (25 male and 25 female) 18–63 years old have been examined with regard to ocular complications After the transplantation they have been treated with corticosteroids and immunosuppressives One year after the renal transplantation a posterior subcapsular cataract (p s c) was found in almost 50 % of the patients After two to three years the frequency of p s c in this group was about 80 % The incidence was somewhat higher in women than in men However the difference was probably not significant since the group was small and the average age of the women was higher than that of the men In spite of the p s c, visual acuity was decreased only slightly in most patients

18 out of 48 patients examined with the Goldman Weeker adaptometer and/or scotoptometer presented a slightly impaired nightvision 24 out of 48 patients examined

with pseudoisochromatic tables (Bostrom II and Bostrom Kugelberg) showed a defective colourvision It is remarkable that 15 of these patients with defective colourvision were women We have only been able to test a few patients with the Nagel anomaloscope and the results were not quite clear The impaired night and colourvision indicate retinal disturbances which might be connected with the therapy since the occurrence of defective colourvision highly exceed what we have found in a preoperative control group It is unlikely that p s c influenced the night or colour vision as all patients except one had a visual acuity of more than 0 7

48 out of 50 patients examined with applanation tonometry at repeated intervals had an intraocular pressure below 25 mmHg Only one patient had a pressure above 30 mmHg thus needing therapy

Among other ocular complications observed were 3 cases of relapsing dendritic keratitis Furthermore several patients presented with a conjunctivitis In 4 cases the conjunctivitis was combined with chemosis regressing when the dosage of corticosteroids was reduced

L Frisen *Facial paralysis experience with an elastic eyelid cerclage*

A method for restoring dynamic function in the eyelids in cases of facial palsy has been described by Arion (*Int Surg* 57 48 1972) According to this procedure, a specially prepared silicone sling with a carefully calibrated elasticity is threaded subcutaneously around the palpebral aperture and fastened in the lateral periosteum The tension is adjusted so that the sling closes the palpebral aperture upon relaxation of the levator palpebrae

Eight patients were operated upon in this way The immediate post operative results were uniformly good but problems occurred later on in several cases The most common problem was loss of fixation of the sling in the medial canthal ligament, with consecutive loss of tension or even migration through the skin in the medial canthus Six to 11 months following surgery two cases had recovered spontaneously and four had a lasting good result Two cases were failures One of these suffered rejection of the sling along nearly all of its length

Although cosmetically and functionally highly satisfactory (especially where facial palsy is complicated by ectropion) more experience is needed before this new procedure can be recommended without reservation

T Jerndal *Effect of tranexamic acid on late hyphaema – a double blind study in cataract surgery*

The postoperative administration of 1 g tranexamic acid three times a day after cataract extraction resulted in a lower incidence of late occurring hyphaema According to a double blind technique on 244 patients the reduction was statistically significant It is concluded that the drug acts by inhibiting intraocular fibrinolytic reactions Tranexamic acid is suggested 1) as conservative therapy in postoperative or post traumatic cases with intraocular re bleeding or 2) as a prophylactic measure after ocular surgery or trauma

K O Skoog O Textorius & S E G Nilsson *Ethyl alcohol induced long term variations of the standing potential of the human eye*

With a new method it is now possible to follow directly long term variations in the standing potential (SP) of the human eye It is known that the SP oscillates with

a frequency of about 2/h in response to a sudden change in illumination of the eye The present paper shows similar SP variations after an oral dose of ethyl alcohol

Method From five volunteers the SP was recorded twice a minute with special very stable calomel electrodes a suction contact lens and d c amplification The volunteers had been adapted for 15 min either to darkness or to 1100 Lux When a stable SP had been registered for 10 min 0 4 g ethanol kg b w was given orally

Results In response to ingestion of alcohol the SP reacted with a marked amplitude oscillation (frequency about 2/h) which was damped and thus very small after 80 min A first peak was reached after 10 min The response was similar under scotopic and under photopic conditions

Conclusions A small dose of ethanol produces very dramatic long term variations in the human SP Oscillations with a frequency of about 2 h seem to be a stereotype way of reacting by the pigment epithelium since both the c wave of the ERG and the SP (both originating mainly in the pigment epithelium) respond with such cyclic changes to a variety of stimuli

G Akerskog & J Snobohm *A new canulated pigtail probe for surgery of the canaliculus*

P Algvere *Vitrectomy through pars plana ciliaris*

Vitrectomy through pars plana ciliaris is rapidly developing into a promising procedure in ocular surgery This method enables operations inside the vitreous space such as removal of pathological tissue and blood (subtotal vitrectomy)

We have used the VISC (vitreous infusion suction cutter) the tip of which has a motor driven rotating edge and is provided with suction and infusion tubes It is equipped with fiber optics that illuminate the vitreous cavity The cavity is examined through a motorized operating microsome (Zeiss OPMI 6) and a corneal contact lens

The indications for vitrectomy are still poorly defined but include vitreous opacities that prevent the formation of an adequate optical image on the retina and vitreous retraction causing retinal detachment Especially non absorbing vitreous haemorrhages of long duration should be considered for vitrectomy The most favourable results are obtained in uncomplicated haemorrhages in the anterior and central parts of the vitreous which under these circumstances usually becomes detached from the retina Remaining adhesions between the vitreous and the retina or optic disc are often associated with fibrous and cellular strands forming posterior vitreous membranes that can cause a traction detachment of the retina When retinal vessels are pulled into the vitreous space as in diabetic proliferative retinopathy a retinal detachment is likely to occur sometimes accompanied by an epiretinal fibroplasia In these cases retinal circulation and function are deleteriously affected Therefore the preoperative *examination should* include ultrasonography *(B scan) high* energy *ERG VER* (visually evoked response) and if possible fluorescein angiography

The surgical complications of vitrectomy are serious They include retinal tear and detachment, haemorrhage or endophthalmitis

Nevertheless the preliminary results obtained are promising in those cases that have sufficient *retinal function Eyes that have lost orientation vision have regained* reading vision Even juvenile diabetics with proliferative retinopathy and fibrous vitreous changes have likewise shown improvement e g visual acuity 0

P Algvere & B Rosengren *Immobilization of the eye with traction suture – A new concept in the treatment of retinal detachment*

When a receptacle filled with liquid is rotated back and forth – like the eyes own movements – a rotatory flow is seen in the liquid if suspended particles are added When a rubber membrane with a small central hole is mounted inside the receptacle a liquid flow can be observed through the hole Translatory movements of the receptacle produce no flow but rotatory movements even if minimal produce flow (Rosengren & Österlin this section p 378) On the basis of these observations we treated retinal detachment by fixation of the eye prior to surgery in order to prevent or minimize the liquid flow through the retinal hole and facilitate the reapposition

Bilateral eye patches and bed rest in the treatment of retinal detachment generally result in preoperative reattachment in 1/5–1/4 of the cases The eyes are nevertheless not immobilized under patches and considerable eye movements occur especially in vertical direction (Ericson *Acta ophthal (Kbh) 39* 222–230 1961) A higher incidence of retinal reattachment was obtained by immobilization of the eye by a traction suture The suture (3–0 Ti cron) is placed under the inferior rectus muscle at its insertion The eye will be rotated upwards and fixed in maximal elevation The suture can be affixed to the skin of the forehead with tape Even most of the horizontal movements will be eliminated The fellow eye is left uncovered

The traction suture was used in 15 consecutive patients admitted to the Karolinska Hospital Fourteen eyes had a rhegmatogenous detachment (± 5 D) one case was secondary to retino choroiditis One of the eyes was aphakic The detachment was limited to one quadrant of the fundus in 1 eye extended to 2 quadrants in 10 eyes and to 3 quadrants in 4 cases

On the day of admission the suture was placed in the manner described above Following bed rest for 2–3 days (1–5) an almost complete reattachment took place in 8 eyes and a considerable reattachment in 5 eyes In 2 eyes no reattachment was seen one of these had the retino choroiditis in the other eye the suture was improperly placed

Surgery consisted of cryo treatment or photocoagulation in most cases combined with an episcleral silicone rod Release of subretinal fluid was performed in those cases in which the buckle did not seal the retinal break Postoperatively the inferior rectus suture was used for 4–5 days (3–7) after which the eye had healed A primary healing was seen in all eyes except the one with the improperly placed suture

JUDICIA DE NOVIS LIBRIS

Sachsenweger Rudolf Kompendium und Atlas der Augenheilkunde fur Medizinstudenten und Arzte VEB Georg Thieme, Leipzig 1976 170 pages 262 figures Price 14 50 DM

This small East German text book of ophthalmology contains an abundance of good illustrations (720 separate representations of which 65 are in colour) The text is exact and concise, but here and there rather too concentrated Pictures and types are extraordinarily small presumably to render the book saleable at a low price

The size choice of subjects and presentation of the book corresponds approximately to the Scandinavian procedure However I do not quite agree with the author on certain points (classification and definitions of glaucoma therapeutic suggestions etc)

The book may be of use to medical students and general practitioners

M S Norn

H J Merte Augenarztliche Fortbildung Jahreskurse fur die praktische Augenheilkunde Bd 4 Teil 1 Urban & Schwarzenberg Munchen 1976 pp 134 DM 40 –

This small volume is intended as part of a concise advice series It comprises seven chapters The first chapter is a presentation of the various aspects of conjunctivitis lignosa including clinical findings electronmicroscopy and therapy The next two chapters are presentations of the diseases of the orbit lids and lacrimal system

The three following chapters concern ocular motility – differential diagnosis of congenital abducens paresis surgical treatment of the retraction syndrome and ocular torticollis (Kopfschiefhaltung) The final chapter concerns neuroophthalmological aspects of cerebral circulatory disturbances

The differently treated topics appear as articles with references to the literature The value is to be seen in the entire series which represent a concrete offer to the practising ophthalmologist

Niels Ehlers

Sauter Jules Jacques Marie Xerophthalmia and measles in Kenya Drukkerij van Denderen B V Groningen 1976 Pages 285 Price $ 10 – or Dfl 25 –

In this Dutch thesis the author shows the main cause of blindness in Kenya is lack of vitamin A and not measles keratoconjunctivitis or other causes as previously believed Measles has only a catalysing effect on the developement of xerophthalmia

The author gives a detailed description of the many children he has investigated thoughout Kenya and compares this with his investigations in Java Indonesia and the Nederlands

The conditions prevailing in Kenya are described by the author – poverty drought, starvation and death among children emigration of the fathers concealment of blind children by their mothers All this is shocking to read about These are some of the many unsolved problems of an undeveloped country

The author concludes that vital staining with rose bengal or lissamingreen is the be t method for the early diagnosis of xerophthalmia and is especially useful in Health Centres and field surveys

The staining is localized to the exposed triangular conjunctival region temporal and/or nasal to the cornea (grade I) around Bitot s spots (if any) and later around the lower limbus of cornea (grade II) around the upper limbus of cornea (grade III) and finally to the whole bulbar and tarsal conjunctiva and the cornea (grade IV)

The vital staining is a safe and specific method for early detection of conjunctival xerophthalmia At the same time it is cheap and easy to perform

The author prefer lissamingreen because it stains more intensely than rose bengal (the diagnosis can be extablished at a distance of 1–2 meters) and sometimes it also stains Bitot s spot Nevertheless the extent of staining is the same as with rose bengal

In xerophthalmia the mucus production is diminished and the goblet cells disappear The BUT (= wetting time of cornea) is diminished These factors are normalized one week after administration of 200 000 to 300 000 I U vitamin A palmitate in oil dosage according to the age of the patient It is sufficient to administer vitamin A twice a year (prize 8 US cents) Many of these children have been treated with local antibiotics without any benefit

In some cases Bitot s spots do not disappear and the smoky pigmentation of conjunctiva seen in the malnourished children remains apparent.

The differentialdiagnosis between xerophthalmia and pemphigoid keratoconjunctivitis sicca measles keratitis trauma gonorrhoea syphilis and onchocerciasis are described.

The author has performed virological examinations and biopsies in cases of measles keratitis and xerophthalmia

The different stages of the disease are described (XN night blindness X 1A and B conjunctival xerosis X 2 corneal xerosis X 3A corneal erosio X 3B corneal ulceration, X 4 scars)

The very time consuming demonstration of night blindness has been performed and levels of albumin globulin retinol beta caroten retinol binding proteins etc have been investigated

The book includes an interesting chapter concerning causes of blindness in 7 schools for blind children (perforating injuries congenital anomalies optic nerve atrophy etc – Onchocerciasis is no longer endemic in Kenya as a result of the 1955 DDT campaign)

There is a very high mortality rate among blind children in Kenya!

The author concludes with some public health aspects Bianual administration of a

single massive oral dose of vitamin A should be given to children at risk (malnourished children suffering from measles fever affections of the respiratory digestive or uro genital tract) This should be given under strict supervision to avoid intoxication. This is considered an emergency measure only

The author claims that nutrition education and promotion of caroten sources etc are the only logical solution to the problem

The book is well illustrated with numerous sketches photographs diagrams and tables Moreover there are 6 double pages each containing 8 picture in colours on the righthand page with corresponding black and white drawings on the lefthand page with detailed explanations of the pictures of the vital stained eyes or biopsies – a very instructive idea!

This book is to be highly recommended to all those interested in the prevention of blindness (xerophthalmia being one of the main causes of blindness in the world!) and to tho e interested in the cornea the conjunctiva vital staining conjunctival mucus and fat and measles etc

Mogens Norn

VARIA

Letter to the editor

Dear Sir!

I understand from Acta Ophthalmologica Supplementum 125 1975 that it is possible to include literature references after the published abstracts I therefore request that the following references cited in the paper A semiquantitative enzyme assay for corneal collagenase be included

Slanskey H H Gnadinger M C Itoi M & Dohlman C H Collagenase in corneal ulcerations Arch Ophthal 82 108 1969

Berman M B Manabe K & Davison P F Tissue collagenase A simplified semi quantitative enzyme assay Anal Biochem 54 522 1973

Sincerely yours

J U Prause

The Third International Corneo Plastic Congress

will be held at the Royal Festival Hall in London on 29th and 30th June and 1st July 1977 For details apply to Mr T A Casey Corneo Plastic Unit Queen Victoria Hospital East Grinstead Sussex England

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NORMAL VALUES IN CLINICAL ELECTROOCULOGRAPHY

II Analysis of Potential and Time Parameters and Their Relation to Other Variables

BY

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The following EOG potential and time parameters from 72 normal subjects were analysed base value *B* dark trough *D* light peak *L* light induced potential rise *L–D* interval between beginning of dark adaptation and occurrence of dark through *d* and interval between dark trough and light peak *l* Their relations to sex age, pupillary diameter degree of iris pigmentation refractive error axial length corneal curvature and diameter ocular protrusion and interpupillary distance were assessed Right eye and left eye samples of the EOG parameters were congruent although individual differences were sometimes appreciable. The levels of *B* and *D* were higher in the female half of the sample A positive correlation existed between age and *D* level *L–D* was negatively correlated to the degree of refractive error and positively correlated to the ocular protrusion A positive correlation was found between *d* and the four potential parameters and there was a positive correlation between age and *l* Practical consequences of the statistical analysis relating to the interpretation of such EOG data are discussed

Key words electrophysiology – electrooculography – EOG – potential parameters – time parameters – normal range – statistical analysis

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The initial event in clinical electrooculography (EOG) consists in an indirect recording of the oscillations of the corneofundal potential (CFP) as evoked by some standard changes in illumination intensity. This usually involves no complications, whereas the subsequent interpretation of the test outcome presents the observer with many as yet unsolved problems, particularly as concerns quantitative statements. The main reason for this is the marked inter- as well as intra-individual variation of the potential figures even for normal eyes (François et al. 1956, Davis & Shackel 1960, Hohne 1974), which have been said to eliminate any information of clinical value from such data (Arden & Barrada 1962, Gliem 1971).

A certain amount of variation is scarcely surprising in view of such badly controlled factors in the recording technique as the distance between the intraocular CFP potential generator(s) and the skin electrodes and the volume conductor properties of the orbital region. Additional sources of variation are conceivable, e. g. in possible relations between the EOG parameters and other anatomical or physiological variables of the subject.

The purpose of the present paper is to study the following potential figures obtained from an EOG investigation of a series of normal human subjects: the base value B measured according to Gliem (1971), the dark trough D, the light peak L and the light induced potential rise $L-D$. Two time parameters, the interval between the beginning of the dark adaptation and the occurrence of the dark trough d and the interval between the dark trough and the light peak l, are also examined. Their mutual relations are traced and the general and individual differences between right eye and left eye values of each parameter are assessed. A subsequent analysis deals with the relationships between these parameters and the following subject- or eye-linked variables: sex, age, pupillary diameter, degree of iris pigmentation, refractive error and axial length, radii of corneal curvatures, corneal diameter, ocular protrusion and interpupillary distance. Finally, the consequences of the results for the interpretation of such EOG data are discussed.

Material

The investigation comprises 142 eyes (72 subjects with an equal number of females and males and an age span of 13–81 years). Details concerning the selection of the sample and its biometrical characteristics are stated in an earlier paper (Krogh 1975a). For convenience the minimum, median and maximum values of the EOG parameters in question are stated: B: 148–368–938 μV, D: 71–238–460 μV, L: 214–562–1251 μV, $L-D$: 71–321–791 μV. The frequency diagram of the last parameter is shown in

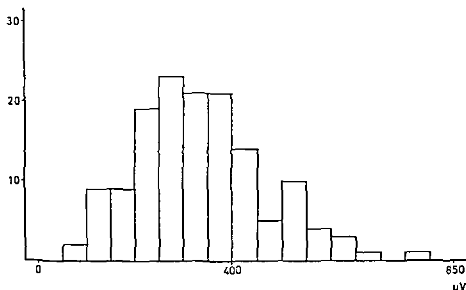


Fig. 1
Distribution of the differences between light peak and dark trough (*L–D*)
class interval = 50 μV

Fig 1 The corresponding diagrams of the three primary potential parameters are found in an earlier paper (Krogh 1975a) The range and median values of the time parameters are *d* ~10–15 min and *l* 5–8–12 min

Methods

RECORDING TECHNIQUE

A detailed description of the EOC procedure is included in an earlier paper (Krogh 1975a) DC amplification (bandwith 0–15 Hz) was employed which ensured that variations in eye movement velocity did not influence the amplitude of the recorder deflections and further that irregularly performed saccades could be measured with accuracy (Krogh 197 b) On the other hand it had the result that only 111 *B* values could be recorded.

STATISTICAL EVALUATION

The distribution free statistical tests were perf rmed by means f EDP (Stat stical Section, R gshospitalet Copenhagen) The hypothes s of no s ale sh ft between two or more sets of data was tested by the following methods Mann Whitney s test for

two independent sets of observations Wilcoxon s test in cases of paired observatio s and Kruskal Wallis test for three or more independent sets of observations The hypothesis of no monotonic relationship in two sets of observations was evaluated by Spearman s rank correlation test expressed as a coefficient (r_s) Finally the hypothesis of equal dispersion around the medians of two sets of observations was estimated by Westenberg s interquartile range test which utilizes Fisher s exact probability test (Siegel 1956 Bradley 1968)

For the discussion, a 0 05 limit of significance was selected but in every in tance the *P* values are stated to the reader s own consideration A two tailed significance estimate was used when two sets of observations were compared or correlated The *H* statistic in Kruskal Wallis test is assessed by an upper tail region of rejection only

Positively correlated data from right and left eyes cannot be treated as independent observations when related to subject linked variables such as age sex and in er pupillary distance In such cases the average of the individual right and left eye values was used in the statistical analysis In two subjects only the one eye fulfilled the criteria for inclusion in the sample and in these cases the sole values were used This procedure halves the number of observations but in return the available data are subject to less variation

Results

RIGHT AND LEFT EYE CONCORDANCE

The differences in the present study between the median values of the right and left eye samples of the parameters *B D L L D d* and *l* were not significant (Wilcoxon s test $P > 0\ 3$ in all cases) Neither were any significant differences

Table I
Numerical right eye left eye differences of EOG potential and time parame ers

	Median value	Maximum value
Base value	48 μV	284 μV
Dark trough	37 μV	113 μV
Light peak	61 μV	476 μV
Difference between light peak and dark trough	51 μV	316 μV
Interval between beginning of dark adaptation and dark trough	0 min	3 min
Interval between dark trough and light peak	0 min	2 min

Table II
Correlations between EOG potential parameters ($P < 0\ 001$ in each case)

	Difference between light peak and dark trough	Dark trough	Light peak
Base value (N = 111)	$r_s = 0\ 74$	$r_s = 0\ 77$	$r_s = 0$ [illegible]6
Light peak (N = 142)	$r = 0\ 90$	$r_s = 0$ [illegible]3	
Dark trough (N = 14[illegible])	$r_s = 0$ [illegible]9		

ound in the degree of scatter around the right and left median values of the otential parameters (Westenberg s test $P > 0\ 2$ in all cases) the class interval f the time parameters was too large to allow a similar analysis Nevertheless *ndividual* right left differences can be of appreciable magnitude as shown by he figures in Table I

Table III
Female and male median values of EOG potential parameters (average of individual right and left eye values)

	Base value	Dark trough	Light peak	Difference between light peak and dark trough
Females	411 μV	67 μV	[illegible]0 μV	337 μV
Males	343 [illegible]V	21[illegible] μV	[illegible]40 μV	[illegible]0[illegible] [illegible]V
Mann Whitney s test	$P = 0\ 03$	P – 0 00[illegible]	P 0 [illegible]	P = 0 [illegible]

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Table I

Numerical right eye left eye differences of EOC potential and time parameters

	Median value	Maximum value
Base value	48 μV	[illegible]84 μV
Dark trough	37 μV	113 μV
Light peak	61 μV	476 μV
Difference between light peak and dark trough	51 μV	376 μV
Interval between beginning of dark adaptation and dark trough	0 min	3 min
Interval between dark trough and light peak	0 min	2 min

Table V
Median dark trough values according to the degree of iris pigmentation
(Kruskal Wallis test, $P = 0.008$)

Classes of iris pigmentation (ascending order)	1	2	3	4
	210 μV	232 μV	250 μV	215 μV

degree of pigmentation (Tocher 1908) Only the class differences of the *D* parameter were significant (Table V) Because of varying sex ratios in the four classes the data from each sex were re analysed separatedly Although Classes 3 still contained the highest *D* levels the differences were now insignificant ($P = 0.5$ for the female part of the sample $P = 0.08$ for the male part)

Degree of refractive error axial length, radii of corneal curvatures, corneal diameter ocular protrusion and interpupillary distance

This study revealed no relationships between these variables and *B* *D* and *L*

The light induced potential rise

Table II lists the correlation coefficients between (L D) and the other potential parameters in this study

The difference between the medians of the female and male groups was not significant (Mann Whitney s test, $P = 0.7$ Table III) and neither was the negative correlation to age ($r_s = -0.16$ $P = 0.2$)

A positive correlation between *L-D* and the pupillary diameter was demonstrated ($r = 0.20$ $P = 0.02$) This appears to accord with the previously established negative correlation between *D* and the pupillary diameter The latter relation was attributed to a common variation with age whereas the parameter *L D* revealed no significant variation with age

A negative correlation was found between the degree of refractive error and *L-D* ($r = -0.20$ $P = 0.02$) This relation was not supplemented by a significant positive correlation between *L D* and the axial length of the eye ($r = 0.04$ $P = 0.4$) The expected relationship was found between the axial length and the degree of refractive error ($r = -0.41$ $P < 0.001$)

A positive correlation was demonstrated between *L D* and the ocular protrusion, measured a. m. Hertel ($r = 0.25$ $P = 0.002$) The remaining variables as listed in the introduction were unrelated to *L D* in this study

Table VI

Correlations between EOG potential parameters and the interval between the beginning of the dark adaptation and the occurrence of the dark trough

Base value	Dark trough	Light peak	Difference between light peak and dark trough
$r_s = 0.30$ $P = 0.001$	$r_s = 0.22$ $P = 0.007$	$r_s = 0.25$ $P = 0.003$	$r_s = 0.17$ $P = 0.04$

Time factors

No mutual correlation existed between d and l. B, D, L and L/D all showed a positive correlation to d (Table VI). No significant d or l differences were disclosed between the female and male groups (Mann Whitney's test $P = 0.3$ in both cases). A positive correlation was revealed between l and age ($r_s = 0.29$, $P = 0.01$). A negative correlation was found between the pupillary diameter and l ($r_s = -0.25$, $P = 0.01$); this relation is in agreement with the joint variation with age of the two parameters. Finally, a connexion was found between d and the degree of iris pigmentation. In Classes 1 and 2 the median d value was 10 min, and in Classes 3 and 4 it was 11 min (Kruskal Wallis test $P < 0.001$).

Discussion

The concordance between the right and left eye distributions of the EOG parameters under study indicates uniform stimulus and transfer conditions. The *individual* right left differences are however in some cases appreciable. The only figures for comparison are found in Gliem's monograph (1971): 15/90 normal subjects demonstrated a right left difference of B of at most 100 μV and the highest difference recorded was 300 μV. This seems to indicate about the same degree of individual concordance in the two studies when it is recalled that the potential level in Gliem's investigation is somewhat higher than in the present study (Krogh 1975a). Gliem also analysed the right left difference of the two EOG time parameters and found no difference in 16/40 (both parameters measuring interval 2–3 min). In the present study the corresponding ratio was 128/140 (measuring interval 1 min). This difference is statistically significant (principle of maximum likelihood, $t = 12.2$, $P < 0.001$).

No sex related differences in potential level were found by François et al (1957) whereas Hohne (1974) found significantly higher potential values in women in all part of the EOG potential time curve The similar difference in the present study was however not significant in the case of *L* but it must be emphasized that Hohne s test sample was larger than that analysed in this study

No connection between age and EOG potential level was found by François et al (1957) whereas Shackel (1960) in a test sample of limited age span (15–17 years) demonstrated a negative correlation ($r = -0\ 33$ $P = 0\ 001$) between age and the bitemporally recorded EOG potential This correlation disappeared however at a re examination 10 months later (Shackel & Davis 1960) Hohne found that the EOG potential levels were higher in a group of 17 year old subjects as compared with a group of 26 year old subjects The latter result agrees with the figures in Table IV but a Mann Whitney test shows that the figures in the first two columns do not differ significantly ($P = 0\ 3$) The marked increase in the *D* values in the older age groups is a new observation which may be explained either by a change in the voltage of the potential generator(s) or by a change in the resistive properties of the tissues in the measuring circuit.

The figures in Table V are difficult to interprete Gahlot & Hansen (1974) examined the EOG s of normal caucasians normal negroes and albinos They found equal base values (not further defined but probably best corresponding to the dark trough potential) among caucasians and negroes but considerably lower values among albinos The proportion of males to females was not stated so that analogies with the present material are difficult to draw

According to the theory of Thijssen & Pinckers (1974) concerning the contra lateral effect of the EOG potential there should be a positive correlation be tween the potential level and the distance between the right and left eye potential generators If it is assumed that this distance is represented by the interpupillary distance with parallel visual axes the present study cannot support the theory

The parameter *L D* is of importance for two reasons 1) The light induced potential rise is the most sensitive EOG parameter in retinal pathology (Arden et al 1962 Gliem 1971) and 2) The CFP is a composite potential A sub stantial part undoubtedly originates in the pigment epithelium receptor complex (Noell 1952 Brown & Wiesel 1958 Foulds & Ikeda 1966 Lasansky & de Fisch 1966) Other sources are however conceivable e g the ciliary epithelium (Berggren 1960) a Donnan potential between the blood and the aqueous (Leh mann & Meesmann 1924) the lens (Brindley 1956) and the corneal epithelium (Arden & Fojas 1962) Pasik et al (1966) even succeeded in recording EOG potentials of normal magnitude a few weeks after bilateral evisceration of

monkey eyes If the sum of the extraretinal voltages is assumed to be more or less constant during an EOG procedure then the parameter *L D* will to a high degree represent the light sensitive generator only

The negative correlation between *L D* and the degree of ametropia is remarkable in view of the absence of a similar correlation between *L* which is highly correlated to *L D* (Table II) and the refractive error Nor does it appear to be secondary to a relationship with the axial length of the eye A study of unilateral myopia and of ≧ 3 dp myopic anisometropia (Alexandridis et al 1975) gives an interesting comment The mean EOG potentials of the more myopic eyes were higher as compared with the fellow eyes and from a diagram (Fig 3) one can estimate that the mean value of *L D* also is higher (about 33 %) in the myopic eyes

The positive correlation between the ocular protrusion and *L D* in the present study contrasts with the negative correlation between the protrusion and the bitemporally measured EOG potential in a study by Mackensen & Harder (1954) Similarly Alexandridis et al (1975) found slightly diminished EOG potentials in unilaterally protruding eyes as compared with the fellow eyes but – estimated from a diagram (Fig 1) – the parameter *L D* did not differ between the two groups

Scanty information is available to illustrate the EOG time factors They were measured by Arden et al (1962) Gliem (1971) and Taumer et al (1974) and their figures agree with those presented in this sample

The EOG potential time curve permits the collection of many data which however do not necessarily reflect a similar quantity of information Thus *B L* and *L D* more or less state the activity of the light sensitive voltage source (Table II) and in clinical application the consideration of only one of these parameters seems a worth while simplification With reference to earlier remarks the quantity *L D* would be a logical choice

A practical consequence of the present investigation is that individual right left differences as enumerated in Table I must be considered as normal with the present recording technique *Samples* of right and left eye values are however congruent and the use of mean or median values instead of single parameter estimates is therefore theoretically although not practically advisable also when individual right left comparisons (or follow up examinations of the same eye) are requested Moreover the relationships here discussed between the EOG parameters and other variables should not suggest any subdivison of the normal reference values in view of the appreciable residual variation In general the present study emphasizes the need for adequate control samples if deductions from clinical or experimental circumstances are to be justified

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A CASE OF LATE PSEUDOMONAS OCULAR INFECTION FOLLOWING SCLERAL BUCKLING

BY

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Two and half years after a circling buckle operation in which two Supramid sutures and a solid silicone explant were employed a Pseudomonas infection developed around the explant and progressed to the inner eye Removal of all implanted foreign material and treatment with Rifamicin saved the eye The relevant literature on infection following scleroplastic procedures is reviewed and the pathogenesis of the late infections is discussed

Key words retinal detachment – scleral buckling – infection – Pseudomonas – Rifamicin

Since the introduction of scleroplastic procedures for retinal detachment repair where foreign material is employed in form of implants or explants with or without an encircling element postoperative infection has remained in many places a distressing complication (Lincoff et al 1965 1970 Regan & Schepens 1964 Russo & Ruiz 1971 Schepens et al 1960 Ulrich & Burton 1974)

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Even with strict adherence to asepsis during surgery contamination cannot be absolutely eliminated and increases with the length and difficulties of the intervention

Recognition of an infection may be difficult in the early postoperative period if there is an undue reaction to the surgical procedure itself Once infection has been recognized an attempt may be made to save the buckle by intensive systemic and local antibiotic treatment But when signs of intraocular involvement are present all foreign material has to be removed without procrastination even at the risk of a redetachment

Late infection seems to be more frequent It may first become manifest months and even years after the surgical intervention Although the patient may complain of pain with a red and tender eye in the interval there are many cases in which the eye has remained entirely asymptomatic up to the time of the acute episode Even in these late instances removal of all implanted material is imperative as soon as signs of an intraocular reaction become apparent. Very often extrusion or exposure of the explant or implant has already commenced

Reviewing the relevant literature we were surprised by the differences in the reported incidence rates of infection following scleral buckling procedures and in particular by the contrasting low incidence of this complication in our unit

We take therefore the opportunity of reporting a peculiar case of late infection following scleral buckling where pseudomonas and not the obligate Staphylococcus was the offending agent

Case Report

A 48 year old patient was admitted to the Eye Department of the Government Hospital Jaffo in October 1969 with a recurrent retinal detachment in her left eye. This eye had been successfully operated on for detachment 20 years previously

On admission visual acuity in the left eye was reduced to hand movements A total detachment with multiple holes at the site of the former detachment operation was present A double cerclage operation (Hauer 1965) was performed using 2 encircling supramid sutures each of which was anchored intrasclerally in each quadrant. After diathermy treatment of the hole area a grooved solid silicone implant (5 × 12 mm) was inserted as an explant under the two circling sutures and secured by additional supramid mattress sutures The retina was reattached Visual acuity improved to finger counting at 2 m The eye remained quiet and the retina reattached for a period of 1½ years

In March 1971 foreign body sensations with intermittent pain and redness in the operated eye were found to be caused by knots of the mattress sutures securing the

explant which had eroded the overlying Tenon's capsule and conjunctiva. After removal of the sutures all complaints vanished. A culture taken at this time from the conjunctival sac was sterile.

Two months later, during which time the eye had remained absolutely asymptomatic, a severe inflammation especially concentrated in the region of the explant brought the patient back to the hospital. On the assumption that the episcleritis-like bulge was a form of allergic reaction to the underlying implanted silicone, an intensive treatment with systemic and local steroid supported by Tanderil (Geigy) tablets was commenced and continued for 4 weeks. Since no obvious improvement resulted from this therapy, the grooved implant was removed in the operating theatre under aseptic conditions and Penicillin and Streptomycin were injected subconjunctivally. The intervention was followed by a severe exacerbation of the inflammation accompanied by flare, posterior synechiae and vitreous opacification. Under treatment with local and systemic steroids slight remissions was achieved but on the whole the condition of the eye deteriorated. In January 1973, in spite of unclear media, it appeared that one or both circling sutures had eroded the ocular wall in the lower half of the eyeball and had migrated into the eye. After removal of a granuloma covering the site of the former explant, the encircling sutures were exposed and despite the risk involved in pulling out a circling element that had migrated into the eye, the sutures came out without any resistance and with them creamy pus poured out of the suture track.

The sutures were put in Brain Heart broth for 24 h at 27°C and the cultures were then transferred to blood agar plates. A strain of Pseudomonas was isolated in pure culture. Its characteristics were:

Acid from			
Glucose 1 % (OFBM)	+	Oxidase	+
Xylose	+	Phenylalanin deaminase	–
Lactose	–	Lipase	+
Sucrose	–	Starch hydrolysis	–
Maltose	–	Deoxyribonuclease	–
Mannitol	+	Gelatin hydrolysis	–
Fluorescence	+	Haemolysis	–
Pyocyanin	–	Growth on McConkey agar	+
Hydrogen sulfid (KIA)	–	Motility	+
Urea	–	Cetrimide tolerance	+
Nitrite production	–	Growth at 42 C	+
Nitrogen gas production	–	Growth at 5 C	–

These characteristics suggested that the isolated bacterium was Pseudomonas aeruginosa (Gilardi 1971). However, it should be noted that the strain was negative in Pyocyanin and nitrite production, resembling in this respect Pseudomonas putida. Sensitivity tests revealed that it was susceptible, though only weakly so, to Rifamicin, and resistant to all other antimicrobial agents.

With intensive treatment by Rifamicin eye drops (Chibret), subconjunctival injections of Rifampicin (Lepetit) and Rifadin (Lepetit) capsules a gradual improvement was achieved. The eye calmed down and the tension which had been reduced during

the acute phase returned to normal Vision remained reduced to correct light projection owing to a dense cataract that had meanwhile developed

Comment and Discussion

While the pathogenesis of an acute infection arising as a consequence of an intraoperative or early postoperative contamination is easily understood an explanation of the mechanism responsible for late infections occurring months and even years after buckling operations meets with some problems It is hardly possible that a pathogen and in our case a highly potent one introduced at the time of surgery should remain dormant for months without any signs of its presence Even the assumption that in the present case the microorganism entered the subconjunctival space at the time of removal of the protruding sutures is not plausible since the eye calmed down and remained entirely asymptomatic for a further ten months It is therefore implied that shortly prior to the acute infection the offending microorganism finds its way into the eye through microscopic openings in the surface covering which are created when the explant or in other cases implant begins to be extruded In the present case the protrusion of the sutures anchoring the explant seem to have been a signal of such an event

Russo & Ruiz (1971) also concluded that infection alone does not fully explain the late complication although bacterial growth was found in all late cultured cases They reasoned that infections with organisms even as slightly pathogenic as Staphylococcus epidermidis or Micrococcus should not require months to become manifest In their opinion mechanical factors play a predominant role and initiate a series of events that ultimately lead to rejection of the implanted material with or without accompanying infection The bulgier an explant or implant the greater the stress by eye movements on the buckling elements and on the sutures fixating them From this point of view buried intrascleral implants should be more protected against the mechanical stress than episcleral explants There is little doubt that infection plays a part in the overall syndrome but apparently its role is only a secondary one since there are cases in which an explant is extruded without any signs of infection or inflammation

Reviewing the literature for the incidence of infection following scleral buckling operations great differences are met with resulting partly from the fact that in many reports the incidence rate relates to specific selected groups of patients Regan & Schepens (1964) reporting on erosions of ocular walls by encircling polyethylene tubing found 40 instances of infection among 141 cases of reoperations due to erosion exposure or extrusion of implants In 1960

Schepens et al abandoned the polyviol explant of Custodis since infection prompted its removal in 6 out of 25 cases with endophthalmitis in 4 of them Reporting from Schepens clinic McMeel (1965) found a positive correlation between the presence of pathogenic bacteria in the wound site at the completion of surgery and the incidence of postoperative infection While only 0 66 % of postoperative infections occurred in eyes where no growth was seen on culture at the time of operation in the group which grew coagulase positive St aureus an infection rate of almost 14 % was encountered No distinction was made between early and late infections Lincoff et al (1965 1970) found a scleral abscess in 5 (3 6 %) out of 137 cases where grooved solid silicone implants were buried in half thickness scleral pockets and in 3 (3 1 %) out of 94 procedures in which a silicone sponge cylinder was sutured over full thickness sclera The infection rate has not significantly declined after the substitution of cryopexy for diathermy but the character of the infection has changed from an abscess with intraocular involvement to that of an extraocular granuloma Russo & Ruiz (1971) presenting the incidence and clinical manifestations of infection and/or rejection of soft silicone sponges in a series of 117 detachment operations had to remove the sponge in 31 (24 4 %) cases in 9 of them because of early acute infection and in the remaining 22 because of late infection In all cases bacterial growth was present in cultures taken from the implants Ulrich & Burton (1974) reported postoperative infection with rejection of a scleral implant in 37 (4 %) of 878 detachment operations In slightly more than half of these cases infection occurred within 3 months and as late infection in the remainder The risk of infection appeared greater when preoperative cultures demonstrated pathogenic flora when the procedure was a reoperation and surprisingly when the buckling element was solid silicone Although agreement between the bacterial findings prior to the operation and those from the infected site was found only in 23 % the authors recommended postponement of scheduled surgery and preoperative treatment with antibiotics if preoperative cultures yield pathogenic flora

Recently Refojo & Thomas (1973) estimating the incidence rate of infection in retinal detachment surgery which employs scleral buckling materials to approximately 2 % were experimenting with impregnation of scleral buckling material with various antibiotics for sustained release Though these measures which included pre intra and postoperative use of antibiotics and strict adherence to asepsis may significantly reduce the rate of early infection it is more than doubtful that they can be considered as a safeguard against late infections for reasons explained before To what extent liberal postoperative administration of steroids which is sometimes excessive increases the susceptibility to infection or aggravates an already existing infection by alteration of

the tissue and conversion of saprophytes to facultative pathogens remains speculative In any case when signs of rejection become apparent cultures from the conjunctival sac should be taken and if positive appropriate antibiotics should be employed

Primed with information from the literature about the incidence of infection following scleral buckling operations as presented above the low incidence rate in our unit was surprising In 1000 retinal detachment operations performed during the last 10 years in the Eye Department of Tel Hashomer the Schepens technique of intrascleral implantation was used in 10 % and in the majority of the remaining cases Lincoff s silicone sponge explants were used There were about 20 % re operations Infection was encountered in only 3 cases one of them following intravitreal injection of contaminated preserved vitreous We cannot but suspect that as yet unknown factors immunologic genetic ecologic or otherwise must be responsible for the difference in the incidence rates It is hardly likely that our technique or asepsis are better

Pseudomonas seems to be the offending pathogen following scleroplastic procedures in exceptional cases The strain isolated in our case was moreover characterised by its resistance to all antibiotics except Rifamicin Administration of this antibiotic in high doses together with removal of all implanted foreign material saved the eye But it has to be stressed that in many cases removal of the implant or explant is all that is required Recurrence of detachment following removal of a buckling element may be as high as 30 %

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SCLERAL BUCKLING WITH BIOPLAST® FIBRIN IN RETINAL DETACHMENT

BY

ISTVAN DE GROSZ, KATALIN VEREB and GEZA KERENYI

The study includes a series of 35 patients with retinal detachment of different aetiology. Scleral reduction combined with the intrascleral implantation of absorbable Bioplast® fibrin scleral buckling rods was performed and reattachment achieved in 31 cases. The implant material is biocompatible and is eliminated from the eye in the course of a few weeks.

Key words: Bioplast® – fibrin – intrascleral implant – retinal detachment

The increasing interest in retinal detachment has lead to improvements in diagnostic and operative techniques. Weve's (1936) scleral corrugation and lamellar resection elaborated by Shapland (1956) increased the cure rate of serious detachments. Schepens (1957) applied encircling in the treatment of extensive detachments. In other methods the vitreous body was filled up with various substances. Dellaporta (1951) and Custodis (1956) proposed the use of implants.

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Several different materials have been used as scleral implants to date These include femoral fascia catgut gelatin collagen polyethylene silicones poly tetrafluoroethylene polyester (Mersilene) etc Some of these implants were found satisfactory but complications have been reported with most of them

Our objective was to test the suitability of fibrin a biocompatible substance for use as an intrascleral implant

Material

Subjects

This study includes a series of 38 patients aged 15 to 72 years They can be divided into three groups according to the origin of retinal detachment There were myopic and traumatic cases and detachments of miscellaneous aetiology Roughly one third of the patients fell into each group

Implant material

Bioplast® is a biocompatible absorbable surgical implant material prepared from stabilized human or bovine fibrin Endoprostheses with various forms and mechanical properties are prepared by the compression moulding of a mixture of fibrin powder glycerine and water The resorption time of the implants can be modified by crosslinking with formaldehyde (Gerendas 1970) The product is airtight sealed in two layers of plastic and irradiation sterilized

No infection fever or undue histological reaction has followed implantation

No clinical symptoms of an immunological response can be detected even after the repeated implantation of the heat deantigenized bovine material The resorption mechanism is identical with that of blood clot organization (Gerendas 1968) The implant is absorbed at an even rate and its metabolites are eliminated mainly with urine (Torok et al 1975) while the site is gradually invaded by autogenous tissue An oncogenic or teratogenic effect has not been observed

Fibrin – generally assumed to play a role in wound healing and regeneration – is thus suited for the temporary replacement of soft and hard tissue

Clinical experience has testified this in hip joint arthroplasty (Kovacs & Gerendas 1961) osteomyelitis (Winter & Papp 1964) female urinary stress incontinence (Horn et al 1975) liver resections (Drobni 1965) retinal detachment (Grosz et al 1967) and oral surgery (Kovacs et al 1976 Kovacs & Kerenyi 1976)

The Bioplast retinal detachment rods are of 0 6 0 8 or 1 1 mm diameter and 20 25 or 30 mm length

The size best suited to the conditions was always selected The rods are flexible but stable enough to cause the choroid to buckle when positioned in the incision down to half the thickness of the sclera On the basis of experience *in animal experiments the resorption time of the rods was set to 3 to 4 weeks* Human fibrin has been used and the implants received as materials for clinical trial

Method

The operations were performed according to one of Dellaporta s methods (Fig 1) After the exposure of the sclera a 3 to 4 mm wide by 15 to 20 mm long sclera strip of half thickness corresponding to the location and size of the *retinal hole was resected (top) parallel to the limbus A Bioplast plug of suitable* size was then placed into the incision (centre) After perforating and semi perforating diathermy the wound edges were drawn together (below) whereby the Bioplast rod is pushed down causing the sclera to buckle in

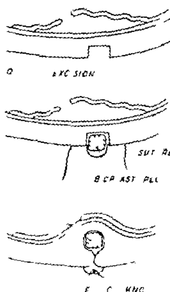


Fig 1
Operative techniques of scleral buckling with Bioplast©

Results

ie clinical course was uneventful in every case For the evaluation of effi ency the 38 subjects have been grouped in three tables according to the igin of detachment

The status on admission is illustrated by a schematic drawing indicating de location and extension of detachment as well as visual acuity Reattach ent the presence of the buckled subretinal strand and visual acuity were con dered as immediate results The last postoperative control varied from between ! days and 3 years Relapses were operated on again if discovered in our epartment but these are not discussed in the present paper

Table I summarizes the operative results of 13 myopic patients The 6 male id / female patients (38 to /0 years of age) were high myopics Their visual uity was determined by the appropriate correction (not indicated in the table ie to lack of space) The fundus was examined 5 and 10 days and one month ostoperatively Reattachment was observed in 10 cases along with a significant nprovement of vision Pronounced buckle with perfect closure of the break as noted 5 and 10 days after the implantation At one month the buckle was

MYOPIA

No	AGE	AT ADMITTANCE: FUNDUS: location of hole and extension of detachment – right	left	AT ADMITTANCE: vision	IMMEDIATE RESULT: vision	FUNDUS: improved	FUNDUS: unchanged	FUNDUS: deteriorated	LAST POSTOPERATIVE CONTROL
1	38			0 25	fc1			+	24 days
2	43			fc1/2	f 3	+			5 months
3	59			fc1/?	fc2	+			2 months
4	61			01	05	+			3 months
5	62			fc1/2		+			12 days
6	58			f	fc3	+			1 month
7	48			fc1/2	fc			+	4 months
8	70			0 3	0 4	+			3 years
9	60			fc	0 3	+			1 month
10	48			fc1/2	0 5	+			1 month
11	44			fc	fc1			+	1 month
12	61			fc1/2	0 5	+			3 years
13	51			0 3	0 3	+			3 months

Table I

Results in myopic cases

TRAUMA

No	AGE	AT ADMITTANCE FUNDUS location of hole and e tension of detachme t		AT ADMITTANCE v s on	IMMEDIATE RESULT s on	IMMEDIATE RESULT FUNDUS			LAST POSTOPERATIVE CONTROL
		right	left			improved	unchanged	deterorated	
1	18			0.9	0.9	+			1 year
2	17			0.2	0.25	+			1 year
3	25			0.3	0.6	+			2 years
4	54			0.2	0.5	+			5 months
5	20			0.25	0.25	+			1 month
6	51			1.0	1.0	+			1 month
7	15			0.15	0.5	+			1 month
8	18			0.2	0.6	+			3 months
9	58			fc1/2	0.3	+			1 yea
10	70			fc	fc1	+			1 month
11	28			0.15	1.0	+			3 years
12	69			fc	fc3	+			1 month

Table II
Results in traumatic cases

in most cases no longer visible and pigmented spots were found in the operative area In three cases the separated retina did not exhibit any tendency towards reattachment

Table II presents the results obtained in traumatic cases Of the 12 male patients 5 were younger than 30 years and 7 fell into the 50–70 years age group The drawings show the size of detachments and the multiple holes seen in most cases The young patients were injured during sporting activities (ball games boxing etc) and the older ones at work This was the most successful group with closure of the tear and reattachment in each case The patients were discharged with good vision with the exception of two cases where haemorrhage of the vitreous body was also present

Table III includes under the title Miscellaneous cases of mixed aetiology These were detachments caused by aphakia haemorrhage of the vitreous body cystoid degeneration etc Of the 13 patients 8 were male 5 were female and their ages ranged from 55 to 72 years In 9 cases the tear was closed by the inwardly bulging implant and reattachment was achieved Two cases were unsuccessful and haemorrhage of the vitreous body with further holes and detachments occurred in another two

MISCELLANEOUS

No	AGE	AT ADMITTANCE FUNDUS location of hole and extension of detachment right	left	vision	IMMEDIATE RESULT vision	FUNDUS improved	unchanged	deteriorated	LAST POSTOPERATIVE CONTROL
1	67			01	09	+			1 mon
2	65			fct/2	03	+			1 y
3	71			03	fc1	+			1 month
4	66			04	05	+			4 months
5	62			02	fc?	+			1 o l
6	56			fc	f 1/2		+		1mo t
7	59			03	04	+			1 mo t
8	58			f15	04	+			weeks
9	67			fc	06	+			1 year
10	55			03	05		+		3 months
11	63			02	fc			+	3 months
12	59			fc	f 1/2			+	2 months
13	72			fc	015	+			3 months

Table III
Results of miscellaneous cases

Histological observations

One of our patients died of a pulmonary embolism 12 days after the operation We thus had the opportunity of studying the implant behaviour histologically and comparing it with other published data (Fig 2)

Sclera

There is a diffuse cellular infiltration consisting mainly of round cells and monocytes among muscle fibres attached to the sclera and superficial scleral fibres A few foreign body giant cells surround the implant which is well on the way to resorption Only fragments of the homogenously stained Bioplast are present

Choroid

The choroidal section above the indented sclera is moderately infiltrated The capillaries are dilated and contain many white blood cells



Fig 2
Section of eye 1? days after Bioplast implantation (haematoxylin and eosin × 30

Retina

Pigment epithelial cells are swollen and in some places *detached* They are located subretinally The retina is supported against the choroid by a homogenously stained substance Retinal structure is unchanged The capillaries are dilated

Discussion

The combination of scleral reduction diathermy and Bioplast implantation was anatomically successful in 31 of the 38 cases (81 5 %) This reattachment rate agrees essentially with results reported elsewhere The operative technique is identical with other scleral buckling procedures The new element involved the use of the Bioplast implant The method is not an alternative to cerclage

and not a substitute for diathermy or cryopexy but can be advantageously combined with these processes

The best results were achieved in traumatic cases Indeed a traumatic detachment is thought of as the most obvious indication for Bioplast implantation as the absorbable implant serves to restore the original conditions

An uncrosslinked scleral buckling rod may be absorbed in less than two weeks To ensure that the implant is not broken down too soon the implants are mildly crosslinked during manufacture

The absorbable implant material is not subject to rejection and is eliminated from the site in the course of a few weeks

The histological reaction is milder than that seen after catgut implantation (Orban 1967) and that caused by other implants

The advanced resorption observed 12 days postoperatively shows that Bioplast is eliminated from the eye in due course Complications such as implant rejection implant displacement or perforation of the sclera which may follow the implantation of plastic materials were not seen in this series

Apart from the biocompatibility of the implant a further advantage is seen in the wide flat indentation of the choroid This inhibits the formation of a dead corner often experienced after catgut implantation Such a dead space filled with exudate and blood could lead to a relapse

The authors have previously used catgut as an intrascleral implant Bioplast has been resorted to on account of its superior biocompatibility and lack of the above mentioned dead spaces following implantation

Acknowledgment

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TRANEXAMIC ACID (AMCA) AND LATE HYPHAEMA

A Double Blind Study in Cataract Surgery

BY

T JERNDAL and M FRISÉN

A double blind study of the effect of tranexamic acid (AMCA) on late hyphaema after cataract surgery is reported A total of 244 patients were included in the study after strict selection It was shown that the incidence of late hyphaema in the treated group was significantly lower at the 5 % level than that in the placebo group The conclusion is made that the fibrinolytic inhibitor tranexamic acid can be used therapeutically or prophylactically to decrease the risk for re bleeding after ocular surgery

Key words cataract surgery – fibrinolytic system – hyphaema – ocular trauma – tranexamic acid

Ocular trauma is often accompanied by haemorrhage in the anterior chamber As a rule these hyphaemas are limited and harmless but a dreaded complication is the secondary bleeding or re bleeding on the third to sixth post traumatic day Every ophthalmic surgeon is also familiar with the hazards of these intraocular re bleedings which may be profuse and recurrent and may even result in a blind painful eye (Jerndal 1970) Therefore the introduction

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Selection of cases

Material

The cataract population admitted for operation in the City of Goteborg is supposed not to differ from that of other areas The patients were selected for participation in the study according to strict criteria All known vascular and haematologic diseases disqualified the patient The highest level allowed for the resting blood pressure was set to 190 mmHg systolic and 100 mmHg diastolic pressure The thrombocytic count had to be between 200 000 and 400 000 per mm^3 Normal haemoglobin value and normal bleeding and coagulation times were required The kidney function was roughly estimated by creatinin in serum which was not allowed to surpass 1 5 mg per 100 ml

Because of these strict criteria approximately only one out of four cataract patients was accepted for the study

The patients were allocated to active or placebo treatment by randomization according to a sequential method (see Appendix) The total number of patients in the study was 244 Another 28 patients were originally selected for the study but were excluded 13 because of lost recording cards six because of administrative mistakes three because of a complication at the surgical intervention and six because of suspected side effects of the therapy

As it could not be excluded that antifibrinolytic substances might have a thrombogenic effect the occurrence of any thrombotic complication during the study would lead to the discontinuation of the test for this individual Any other relevant side effect suspectedly due to the drug would also lead to a discontinuation If the cataract extraction was complicated by vitreous loss the case was excluded The patients selected were then subjected to the double blind study and treated for seven days during hospitalization

Administration of the drug

The intake of tablets started at lunch time immediately after the operation 2 tablets of either tranexamic acid or placebo were administered three times daily The tablets were similar in colour shape and taste Each tablet of the active substance contained 0 5 g tranexamic acid Thus each patient treated with active substance received a total of 3 g per day corresponding to 21 g for the whole treatment period Any side effect considered relevant in relation to the drug was noted on the record Well known side effects of tranexamic acid are mild nausea loose stools and rarely orthostatism

Method

The patients on study were examined at the slit lamp microscope once daily during the first seven days Every preexisting hyphaema on Day 1 and sub sequent re bleeding in the anterior chamber were noted on a special day to day record card The quality of the aqueous flare was also observed and re corded e g fine homogeneous corpuscular or distinctly haemorrhagic The appearance of haemorrhagic flare in the course of the study was noted as a bleeding

Statistics

The populations for which the statistical conclusions of this study are valid are defined by the type of cataract patients admitted by the rules of selection (see above) and by the two therapeutic regimes

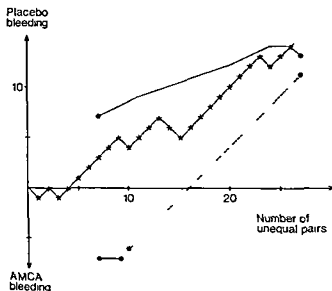


Fig 9

Plan and result of the sequential analysis When one placebo treated member of a pair demonstrated a hyphaema a mark was plotted in the diagram one step to the right and obliquely upwards If an AMCA treated member bled the mark was plotted one step to the right and obliqu ly downwards If the path crosses one f the solid borders (as in the present case) a significant difference (at the • level) is established If the path crosses the broken line H_0 is not rejected Th path will necessar ly cross either border

For each subject the occurrence or absence of re bleeding is registered The frequencies of re bleeding are notated by π_A and π_P for the AMCA and placebo populations respectively

The hypothesis H_0 to be tested is

$$H_0 \quad \pi_A = \pi_P$$

against the alternative that they are different The alternative $\pi_A < \pi_P$ is of much greater interest than the alternative $\pi_A > \pi_P$ as the latter a priori is not considered probable This motivates a skew design as will be discussed below

No factors were known that would greatly vary with time but as a precaution the randomization of treatment was restricted so that pairs with different treatment were constructed from consecutive patients

At the planning stage the number of acceptable patients each year was judged to be small (and turned out to be still smaller) It was thus important to make the sample size no larger than absolutely necessary in order to be able to terminate the investigation in reasonable time These factors motivated the use of a sequential analysis where the data are analysed after each new observation and the investigation is ended as soon as enough information is obtained An exact comparison between the required sample sizes for sequential and ordinary non sequential experiments is hampered by three facts Firstly the sequential sample size is not determined before the experiment but is random Secondly the expected sample size in the sequential case is dependent on the actual values of the unknown parameters Thirdly the calculation of the required sample size is not trivial even in the non sequential case (Frisen 1975) However for some common situations about half the sample size can be expected to be required in the sequential case as compared with the fixed sample size case

A drawback with an ordinary sequential plan is the possibility (however slight) that the sample size turns out to be very large In order to avoid this a restricted plan was used The maximal number of unequal pairs was set to 27 which corresponds to an expected number of about 300 patients under the assumption $\pi_A = 0.05$ $\pi_P = 0.15$

A skew design was used This means that the power to detect the a priori less probable alternative $\pi_A > \pi_P$ is low unless π_A is much greater than π_P This design has the advantage compared with a two sided design that a smaller sample size is required Compared with a one sided design it has the advantage of a built in stopping rule which ends the experiment if π_A is much greater than π_P a case where continuation would be unethical

The significance level was chosen to be 5 %

The power of a design to detect a difference between the two treatments

is of importance for the choice of design It is desirable to be able to make some meaningful conclusions from the experiment even if no statistically significant difference is established but instead the broken line of the plan in the figure is crossed If and only if the power to detect all medically important alternatives (e g in respect of future therapy) is reasonably high but H_0 is not rejected then has the experiment supported the conclusion that there are no medically important differences The power is no simple function of the difference $\pi_P - \pi_A$ but is here illustrated by examples of combinations of percentages π_P and π_A which correspond to a power of about 0 95

π_P	10	15	20	25	30
π_A	2 1	3 2	4 2	5 4	7 5

As earlier described only patients without certain complications of the surgery or suspected side effects were to be studied Nine subjects (three placebo treated and six AMCA treated) had such complications It should be noticed that the inference below concerns a population which excludes this kind of cases Because of administrative mistakes (mainly cards lost at the clinic) 19 subjects (12 placebo treated and seven AMCA treated) which originally were included in the study could not be included in the analysis This exclusion was judged to be completely random as concerns the factors under study The lost cases were replaced by new consecutive ones

The design of the experiment (according to Armitage 1960) and the results are illustrated in Fig 2 A significant difference (at the 5 % level) between π_A and π_P was demonstrated A total of 122 patients were subjected to each treatment Of these 16 4 % of the placebo treated subjects had a re bleeding but only 4 9 % of the AMCA treated ones

Results

The results are graphically illustrated in Figs 2 and 3 The total number of patients suitable for statistical analysis was 244 122 pairs Totally re bleeding occurred in 26 patients 20 turned out to be treated with placebo (20/122) and six with tranexamic acid (6/122) The hypothesis that the placebo group would contain more bleeders than the tranexamic acid treated group was supported early in the study by the trend of the successively plotted graph in the diagram The study lasted six and a half years The final outcome means that a statistically significant difference exists between the placebo group and the tranexamic acid treated one at the 5 % level

Table I
Incidence of hyphaema after cataract extraction (after François & Theunis 1966)

Author	No of operations	Percentage with hyphaema
Vail (1941)	1185	7
Arruga (1946)	not stated	5–20
François (1946)	415	7
Owens (1947)	2086	9 3
Dubois Poulsen (1950)	649	21 4
Rintelen (1951)	173	21
Sedan (1951)	1382	23 94
Legrand (1953)	114	29 82
Saint Martin	1817	19 91

Table II
Suspected side effects

Complications	No of cases			
	Placebo		Tranexamic acid	
	Drug withdrawn	Drug not withdrawn	Drug withdrawn	Drug not withdrawn
Loose stools		2		2
Vomiting and diarrhoea		1		
Vomiting			2	
Marked fatigue			1	
Syncope	1			
Giddiness		1		
Urticaria	1			
Elevated IOP with steamy cornea	1			
Dysuria		1		
Total	2	5	4	2

Side effects

All suspected side effects of the treatment are given in Table II

In the tranexamic acid treated group were four cases with gastro intestinal disturbances none serious The administration of the drug was interrupted in two cases only One patient complained of marked fatigue but recovered promptly after withdrawal of the drug One male patient aged 65 developed a dysuria due to cystitis which was regarded as purely coincidental Also in this case the drug was withdrawn No case of thrombotic complication was encountered There was no tendency to increased intraocular bleeding after the end of the treatment

The placebo group demonstrated three cases of gastrointestinal disturbances and one case each of giddiness syncope and urticaria In the two latter cases the administration of the placebo drug was interrupted The urticaria was thought to be caused by a barbituric acid used as night hypnoticum One patient developed a postoperative elevation of IOP with steamy cornea The tension was normalized by medical therapy No case of thrombosis was observed

Thus only few and no serious side effects after tranexamic acid treatment were observed in this study and there was no certain difference between the tranexamic acid and the placebo groups

Discussion

The therapeutical possibilities for surgical or traumatic intraocular re bleeding have so far been very poor Binocular padding and rest in bed for one week has been suggested and refuted Topical steroids have also been suggested but the result to check re bleeding has not been convincing Irrigation of the blood filled anterior chamber with fibrinolysinic agents has been suggested (Scheie Ashley & Burns 1963) but its clinical value is doubtful

In a survey of postoperative hyphaema after cataract extraction François & Theunis (1966) have accumulated the incidence reported by various authors (Table I) They conclude that the pronounced variation in incidence is probably due to lack of distinction between haemorrhage appearing during the surgical intervention and late haemorrhage appearing on Day 3–7 after operation As for the postulated site of the bleeding they favour the scleral incision but cannot exclude the iridectomy

A number of authors are unanimous that the spontaneous re bleeding usually occurs on Day 3–7 after operation most often on Day 4 François & Theunis

(1966) state that if the bleeding occurs on Day 9 or later or if it is recurrent, a poorer prognosis can be anticipated as the risk for secondary glaucoma and haemato cornea is increased The resorption of the hyphaema takes place gradually probably due to intraocular fibrinolysis (Franceschetti & Eichenberger 1959)

With the discovery of the local intraocular fibrinolytic system a new clue to the understanding and therapy of post traumatic re bleeding was presented Various compounds have been elaborated which could depress the fibrinolytic system

The findings of the present study support the idea that an intraocular fibrinolytic system is at play postoperatively The significantly reduced incidence of postoperative bleeding in the tranexamic acid treated group suggest that this system can be influenced by the drug Nilsson & Rybo (1967) have demonstrated a better antifibrinolytic effect with 6 g tranexamic acid per day compared with 3 g per day in menorrhagia Therefore it is possible that this higher dose might have further reduced the incidence of late hyphaema in the present study

The possible therapeutic applications in ophthalmology of the antifibrinolytic effect of tranexamic acid are thus evident In cases of ocular trauma, either accidental or surgical tranexamic acid can be used to reduce the risk for late haemorrhage A significant effect of AMCA in reducing the incidence of secondary haemorrhage after traumatic hyphaema was recently reported by Bramsen (1976) The indication is particularly strong in cases of established or threatening re bleeding or in individuals where the last eye is operated on or traumatized

As the observed side effects of tranexamic acid were harmless and reversible prophylactic use in severe ocular trauma may be tried

Another conclusion made possible from this study is the postoperative incidence of intraocular haemorrhage in a selected material of healthy cataract patients To 122 patients placebo tablets were given and 20 of these demonstrated a late hyphaema in the control period of seven days Thus the incidence of re bleeding in this material was 16 4 % This figure is relatively high compared with most reported figures in the literature in view of the strict selection of participants for the study Two possible explanations are forwarded firstly the controls were performed daily at the slit lamp microscope and thus any increase in a pre existing hyphaema was disclosed and recorded Secondly also microscopic bleedings presenting as haemorrhagic flares were discovered and registered as bleedings These microscopic bleedings were in minority six placebo cases and one case treated with tranexamic acid (Fig 3)

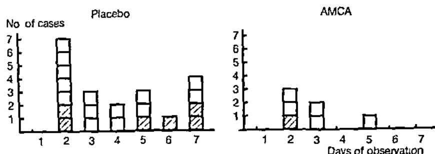


Fig 3
Incidence and chronology of re bleedings Filled squares designate microscopic haemorrhage

The time of occurrence of the re bleeding is also worth a comment (Fig 3) In the placebo group a peak of seven cases is seen on the second postoperative day but still on the seventh day four re bleedings occurred It was also noted that two cases bled on both Day 2 and 3 (These cases are registered on Day 2 only) In the tranexamic acid treated group the peak is also on Day 2 but consists merely of three cases No re bleeding was observed after Day 5 and no recurrent re bleeding was noted

An interesting observation in a number of cases in the tranexamic acid group was the coagulation of a primary postoperative hyphaema which did not seem to hamper its resorption This observation is interpreted as a visible evidence of the depressed intraocular fibrinolysis by tranexamic acid

Conclusions

The postoperative administration of 1 g tranexamic acid three times a day after cataract extraction gave a statistically significantly lower incidence of late occurring hyphaema at the 5 % level

The conclusion is made that the drug probably acts by inhibiting local fibrinolytic activity in the eye

Tranexamic acid may be suggested 1) as conservative therapy in post operative cases with intraocular re bleeding or 2) as a prophylactic measure after ocular surgery

Acknowledgment

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EFFECT OF ORALLY ADMINISTERED HYDROCORTISONE ON THE OCULAR TENSION IN PRIMARY OPEN ANGLE GLAUCOMA SUBJECTS

Preliminary Report

BY

RYOZO KIMURA and NOBUO MAEKAWA

We studied the possible influence on the pattern of diurnal ocular tension curve by peroral hydrocortisone in 16 eyes of 16 subjects with primary open angle glaucoma. The baseline diurnal curve was determined by Schiotz tonometry six times daily starting at 10 a.m. and repeated every four hours. The baseline curve showed a significant rise in the daytime with a fall during the night. On another day 20 mg hydrocortisone was given perorally at 5 p.m. for a repeat 24 h measurement period. A significant rise in ocular tension over the baseline resulted in the following night time tonometric readings i.e. at 10 p.m. ($P < 0.01$) and 2 a.m. ($P < 0.001$). The results seem to strongly indicate that plasma corticosteroid levels dictate the pattern of diurnal variation of ocular tension.

Key words: ocular tension – intraocular pressure – diurnal variation of ocular tension – corticosteroid – hydrocortisone – oral hydrocortisone test – primary open angle glaucoma

Ericson (1958) confirmed by means of a suction cup method that aqueous humour inflow showed twenty four hourly variations with a minimum during the night. It is widely accepted that plasma cortisol reaches its peak in the early morning and thereafter declines throughout the day reaching its low point

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at midnight (Pincus 1943 Bliss et al 1953) Linner (1959) reported that the ocular tension and the rate of aqueous flow were significantly elevated after topical application of corticosteroid while no significant changes were found in both episcleral venous pressure and scleral rigidity Therefore he supposed that there might exist some connections between the rate of aqueous flow and the plasma cortisol levels Boyd et al (1961) reported that there was a parallelism of diurnal variation of ocular tension and plasma corticoids in the majority of glaucomatous subjects They (Boyd & McLeod 1964) also reported that SU 4885 which interrupted the rising phase of plasma corticoids also interrupted the rising phase of ocular tension Smith et al (1962) reported that the diurnal rhythms of plasma 17 hydroxycorticosteroids and ocular tension appeared quite similar in man However we are unable to exclude not only the probability of occurrence of simultaneous change in plasma cortisol levels and ocular tension but also the probability of direct effect of SU 4885 or 11 desoxycortisol on ocular tension Therefore it seems indispensable to directly prove a rise of ocular tension by means of systemic corticosteroid administration Kimura (1974) examined the day to day variation of ocular tension in a case of glaucoma induced by systemic corticosteroid therapy sequentially changing the time of corticosteroid administration – either at 5 p m or 8 a m When corticosteroid was administered at 5 p m a rise of ocular tension following the administration of corticosteroid seemed to be encountered Weitzman et al (1975) found in a case of pigmentary glaucoma that in spite of total suppression of cortisol secretion by means of intravenous administration of 2 mg dexamethasone at 8 p m the diurnal ocular tension curve on the following day was still present However although they did not discuss the effect of intravenously administered dexamethasone itself on the ocular tension a rise of ocular tension during the night after the administration of dexamethasone seemed to be shown in their Fig 6 The purpose of this communication is to report the effect of perorally administered hydrocortisone on the ocular tension in primary open angle glaucoma subjects

Materials and Methods

We selected primary open angle glaucoma patients from our clinic All patients had a complete eye examination A subject was disqualified if the anterior chamber angle was not wide open (grade 3–4) in all quadrants according to Shaffer s classification (1962) Subjects with a history of ocular surgery and ocular trauma and with significant ocular disease other than senile cataract were excluded 16 subjects 9 males and 7 females were selected for this study The age of the subjects ranged from 10 to 54 years (mean age 26 9 median age 23 5)

Table III

Statistical comparison among mean ocular tension in the control period (probability of chance < 0.05)

Time in hours	10 a m	2 p m	6 p m	10 p m	2 a m	6 a m
10 a m		–	–	< 0.001	< 0.001	< 0.05
2 p m			< 0.01	< 0.01	< 0.001	< 0.05
6 p m				< 0.01	< 0.01	–
10 p m					< 0.05	–
2 a m						< 0.01
6 a m						

Table IV

Statistical analysis of mean difference in ocular tension between control period and hydrocortisone trial period (probability of chance < 0.05)

Time in hours	10 a m	2 p m	6 p m	10 p m	2 a m	6 a m
Mean difference in ocular tension (Mean ± SD) mmHg	+1.94 ± 7.17	−1.[illegible]5 ± 7.06	+2.31 ± 6.90	+7.75 ± 7.57	+6.75 ± 4.56	+3.13 ± 6.89
Probability	–	–	–	< 0.01	< 0.001	–

& Swanljung (1951) Since then two other methods have been reported by Hager (1958) and Katavisto (1964) Langley & Swanljung (1951) have pointed out that the shape of the curve of the diurnal ocular tension variation is characteristic of the individual in the majority of cases (72 %) By means of Goldmann s modification of Hager s classification (1960) it was revealed that the day type occupied the majority (72 %) Kimura (1972) has developed a new simple method of classification The type of diurnal curve was classified into four types according to the time of the peak pressure namely the day type night type early morning type and combined type According to this classification it was found that the day type was the most frequent (70 %) in 174 eyes out of 100 cases with open angle glaucoma i e in cases of open angle glaucoma the peak pressure was most often encountered during the daytime Henkind et al (1973) noted that the lowest ocular tension was encountered around 3 a m in five normal subjects and six subjects with various types of glaucoma Kitazawa & Horie (1975) also noted that the ocular tension was highest during the day in most subjects (24 normal eyes 28 ocular hypertensive eyes and 27 primary open angle glaucoma eyes) In present study we also showed more clearly that in primary open angle glaucoma the ocular tension in the daytime (at 10 a. m and 2 p m) was significantly higher than the ocular tension at 10 p m 2 a m and 6 a m In other words it was revealed that the diurnal ocular tension variation seemed to have periodicity the pattern of diurnal ocular tension variation had a similarity to the pattern of diurnal plasma cortisol fluctuation (Boyd et al 1961 Smith et al 1962 Weitzman et al 1975) The present study was undertaken in order to clarify the relationship between the ocular tension and the systemic corticosteroid levels Hydrocortisone (20 mg) was administered perorally at the time when plasma cortisol levels were presumed to be at their lowest and a significant rise in ocular tension following the administration of hydrocortisone was encountered From these results it is strongly suggested that the diurnal cycle of plasma corticosteroid levels dictates the pattern of the diurnal ocular tension variation

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A SIMPLE RELATIONSHIP BETWEEN THE PROBABILITY DISTRIBUTION OF VISUAL ACUITY AND THE DENSITY OF RETINAL OUTPUT CHANNELS

BY

L FRISÉN and M FRISÉN

Throughout the retina the parameters of the probability distribution of visual acuity for monochromatic interference fringes are closely proportional to the number of retinal ganglion cells per degree of visual angle There are no simple relationships to receptor spatial frequencies These findings suggest that neuro retinal acuity is determined principally by the spatial frequency of neural output channels

Key words visual acuity – visual fields – optics of the eye – retinal anatomy – threshold definition

Many factors are known to influence on the visual capacity for discrimination of detail It is very likely that the density of neural channels in the retina is one of the most important limiting factors The relationship between acuity and channel density has not yet been elucidated however (Lit 1968 Westheimer 1972)

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A classical hypothesis that sometimes is applied to the fovea and parafovea implies that two minute visual targets can be discriminated as soon as their retinal images are separated by one cone diameter An unstimulated cone may then be left in between two stimulated ones and this has been proposed as a sufficient requirement for discrimination (von Helmholtz 1911 Green 1970) This superficially appealing hypothesis is not only difficult to test because of the intricate characteristics of point source images but is actually incompatible with the stochastic nature of visual discrimination What is required to illuminate the relationship between visual acuity and retinal anatomy is a more comprehensive approach involving the probability of discrimination and accurately defined retinal images The novel interferometric technique fulfils the latter demand the patterns of light/dark cycles have known spatial frequencies and the distribution of light across the pattern is truly sine square Furthermore interferometry is little influenced by the optical faults of the eye (Le Grand 1935 Campbell & Green 1965 Enoch & Hope 1973) and may be considered to measure neuro retinal acuity Optical faults contribute markedly to the peripheral decline in acuity (Frisén & Glansholm 1975)

For any retinal locus acuity for interference fringes can be characterized by the probability of discrimination as a function of the spatial frequency ν_F of the fringes (in cycles/degree) in the form of a sigmoid frequency of seeing curve A simpler and widely used definition is the ν_F which is detected with a certain fixed probability P e g 50 % However there exists no intrinsically natural value of P a fact which often escapes attention

A simple hypothesis relating neuro retinal acuity to retinal architecture is that the probability of discrimination depends only on the image frequency ν_F and the spatial frequency ν_C of neural channels or simpler still only on the ratio ν_F/ν_C The dimension of ν is units per degree of visual angle Provided that the distribution of ν_F is normal the probability of discrimination is fully characterized by the parameters μ (average) and σ (standard deviation) of frequency of seeing curves Under the ratio hypothesis just defined both μ and σ are proportional to ν_C i e their relations to ν_C are linear through the origin Under the assumption of a normal distribution this is not only a necessary condition but also a sufficient proof for the ratio hypothesis

The aim of the present investigation was to analyse to what degree the ratio hypothesis determines neuro retinal acuity The analysis was performed by examination of the proportionality conditions for μ and σ using frequency of seeing data on neuro retinal acuity in various locations in the visual field and data on densities of receptors and ganglion cells (input and output channels) in corresponding retinal areas

Methods

Acuity for monochromatic ($\lambda = 632\ 8$ nm) interference fringes was determined at each 10th degree of eccentricity relative to the center of the pupil on the horizontal meridian The space average luminance of the sinusoidal fringes was 11 cd/m the contrast was maximal and the two observers were well trained – this ensures that the data can be taken to represent maximal neuro retinal resolving power The equipment and the procedures are fully described else where (Frisen & Glansholm 1975) Frequency of seeing curves were established and μ and σ were estimated by probit analysis The relation between μ and eccentricity is given in Fig 1 A

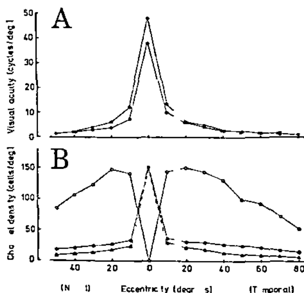


Fig 1

Neuro retinal acuity and distribution of neuro retinal input and output channels measured along the horizontal meridian of the eye. All angular data apply to the center of the entrance pupil

A Average acuity levels at designated locations for two normal subjects The temporal gaps in the curves correspond to the projection of the optic nerve head

B Distributions of receptors (rods o cones ●) and ganglion cells △ projected into visual space. Anatomically there are no ganglion cells in the foveal center but the functional density equals the cone density (interrupted curve)

Density of neural channels. Calculations were based on O'Brien's (1951) observations on the size of foveal cones, Østerberg's (1935) data on extrafoveal rod and cone densities, and Oppel's (1967) counts of retinal ganglion cells along the horizontal meridian. Lacking experimental data on the relationship between eccentricity in the visual field and position on the retina, we made calculations on a wide angle model eye. The calculations were based on the relationship between external (α) and internal (ε) angles derived by Lotmar (1971) and a spherical retina of 12 mm radius. The radial length L_α of each cell counting area was obtained by linear interpolation from Lotmar's Fig. 7. Noting that tangentially limiting rays do not change meridional plane upon refraction, it can be proved that sin 0.5 W ≈ (sin α/sin ε) sin 0.5 W', where W is the tangential width in angular units. $L_\alpha \times W_\alpha$ then is a measure of the counting area's solid angle A in visual space subtended at the center of the pupil. The number of cells N in each area being known, the spatial frequency in visual space is obtained as $(N/A)^{1/2}$, assuming a square packaging pattern. Drasdo & Fowler (1974) independently have derived other formulas leading to the same result.

The density ν_c in visual space for input (rods and cones) and output (ganglion cells) channels at locations corresponding to eccentricities of known acuity could then be determined. A complication arises in the fovea, as the ganglion cells belonging to foveal receptors are displaced to the foveal periphery. The "effective" ganglion cell density of the foveal center can be approximated as the cone density, however (Missotten 1974). The effective receptor and ganglion cell densities in cells per degree of visual angle along the horizontal meridian are given in Fig. 1 B.

Results

By comparing Figs. 1 A and B it is obvious that neither the density of rods nor the density of rods plus cones are simply related to our acuity data. This is not surprising since the light level used in the acuity study exceeds the working range of rods. The proportionality conditions for μ, σ and ν_c therefore were examined for cones and ganglion cells only. The calculations were made on the reciprocal values to avoid excessive weight of the foveal data. The relationships are illustrated in Figs. 2 A-D. The least squares regression through the origin was calculated for each one of these four cases, and the degree to which the slope of the regression function explains the variance was determined (Brownlee 1965). The results are summarized in Table I.

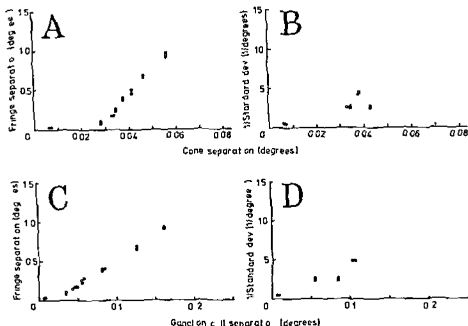


Fig 2

Relationships between reciprocal values of acuity parameters and cone and ganglion cell spatial frequencies Open and closed circles represent the two subjects of this study

Table I

Regression coefficients and per cent unexplained variance for the least squares regression through the origin for $Y = 1/\mu$ and $1/\sigma$ upon $\lambda = 1/s_C$ for cones and ganglion cells

Cell type	Y	Regression coefficient	Unexplained variance (%)
Cone	$1/u$	11 7	34 9
	$1/\sigma$	15 4	53 9
Ganglion	$1/u$	[illegible] 96	[illegible] 5
	$1/\sigma$	43 6	49

The two proportionality conditions are poorly satisfied by the cones. The ratio hypothesis is thus not useful for explaining the relationship across the retina between acuity for interference fringes and the spatial frequency of cones. It may still apply for the parafovea, however (Green 1970, Enoch & Hope 1973).

The situation is different for the ganglion cells. The slope of the regression through the origin of $1/\mu$ upon $1/\gamma_G$ explains all but 7.8 % of the variance, i.e. no more than 7.8 % is due to stochastic and possible systematic errors. This is a remarkably close fit considering the fact that the acuity values were obtained from only two eyes and that these values were related to the average spatial frequencies of five histologically processed eyes *via* theoretical calculations on a schematic eye. Using crude estimates of the ganglion cell separation *within 30° of eccentricity and conventional acuity targets Weymouth (1958)* also arrived at a conclusion of close proportionality.

However, the proportion of unexplained variance for σ runs nearly as high as for cones (Table I). Examination of Figs. 2 B and D suggests that the causes are different: in the case of cones it appears that the unexplained variance is largely due to a poor fit of the ratio model, while in the case of ganglion cells it appears to be due mainly to scatter. It seems reasonable to conclude that proportionality between $1/\sigma$ and $1/\gamma_G$ is not disproved for ganglion cells. The nature of the data cautions against the use of statistical tests for significance.

Thus, in spite of the uncontested complexity of vision and the numerous sources of variance that enter into this type of analysis, the simple ratio hypothesis is able to explain the relationship between visual acuity and retinal architecture in the normal eye throughout the retina: photopic acuity for monochromatic interference fringes of high contrast is principally determined by the spatial frequency of retinal ganglion cells.

Discussion

It should be of no surprise that it is the spatial frequency of *retinal output* cells (ganglion cells) that determines visual acuity, rather than the spatial frequency of retinal input cells (rods and cones). Outside the fovea several receptors converge upon single ganglion cells, forming receptive fields. Receptive fields also occur in the fovea itself. Obviously, it must be the *ganglion cell* that relays positional information to the brain.

It is tempting to try to estimate the density of channels necessary for discrimination by means of the regression coefficient in the relation between $1/\mu$ and $1/\gamma_G$. But the numerical value of the regression coefficient is *in part*

determined by the probability level P used in the calculations (μ corresponds to $P = 50\,\%$) As there is no intrinsically natural value of P a discussion of numerical values has little merit

Another factor contributing to the numerical value of the regression coefficient is the proportion of active neural channels There is no obvious reason to believe that all channels participate in all types of visual tasks Several morphological and functional types of ganglion cells are known and some of these project outside the geniculo striate system (Stone & Fukuda 1974 Levick 1975 De Monasterio & Gouras 1975)

The present analysis does not depend on the information processing that occurs between the receptor layer and the layer of ganglion cells within the receptive fields This processing may well result in neural codes of considerable complexity However it is difficult to conceive of a neural signal pattern capable of telling the brain along one neuron what the details of a stationary retinal image falling on a receptive field looks like It is more likely that an array of differentially stimulated neurons is required for this task and that the spatial frequency of channels limits acuity for immobile targets The situation is quite different for moving targets (Wassle & Creutzfeldt 1973) Many types of visual tasks also have a lower threshold for moving objects at least in peripheral vision

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EFFECTS OF PHOSPHOLINE IODIDE ON THE METABOLITES OF THE GLYCOLYTIC PENTOSE PHOSPHATE AND SORBITOL PATHWAYS IN THE RABBIT LENS

BY

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Steady state concentrations of the key intermediates from the glycolytic, pentose phosphate and sorbitol pathways as well as the pyridine nucleotides were measured from the lens after 0 25 % phospholine iodide had been instilled into rabbits eyes twice a day for 15 weeks In the lenses of those rabbits which had received treatment in both eyes fructose 1 6-diphosphate and pyruvate levels were increased whereas 6-phosphogluconate sorbitol and α glycerophosphate concentrations were decreased α ketoglutarate and concentrations and ratios of NAD^+ and NADH did not show any changes In contrast NADPH and total NADP concentrations as well as the $NADPH/NADP^+$ ratio were decreased and therefore total NAD total NADP ratio increased after treatment It appears that instillation of long acting 0 25 % phospholine iodide into rabbits eyes results in increased glycolytic activity in the lens in response to the increased energy demand whereas the activities of other metabolic pathways are suppressed

Key words phospholine iodide – echothiophate iodide – lens metabolism

Unusual abbreviations NAD(P) nicotinamide adenine dinucleotide plus nicotinamide dinucleotide phosphate FDP gructose 1 6-diphosphate α GOP α glycerophosphate 6 1 G 6 phosphogluconate α KG α ketoglutarate

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Phospholine iodide a long acting cholinesterase inhibitor has been shown to initiate or accelerate cataract formation in glaucomatous eyes (Axelsson 1969 Axelsson & Holmberg 1966 DeRoetth 1966 Pietsch et al 1972 Shaffer & Hetherington 1966 Tarkkanen & Karjalainen 1966 Thoft 1968) Transient clouding of the lens has also been observed in eyes of young persons who have been treated with phospholine iodide for accommodative esotropia (Axelsson & Nyman 1970 Harrison 1960) In our previous study (Härkönen & Tarkkanen 1970) phospholine iodide was instilled into rabbits eyes for 15 weeks and the major components of the energy reserves of the lens were measured ATP was found to be decreased by 35 % and lactate by 17 % whereas glycogen glucose and glucose 6 phosphate did not show any significant alterations Interference with glycolysis or oxidative phosphorylation was suggested as the possible mechanism Interestingly enough decreases of both ATP and lactate were also found in the contralateral untreated eye when the drug was applied to one eye only

Weak acetylcholinesterase activity has been shown to be present in the anterior part of the lens Treatment with phospholine iodide results in complete inhibition of the enzyme activity (DeRoetth 1966 Michon & Kinoshita 1967 Tarkkanen & Härkönen 1969) However the role of cholinesterase in the lens is not known Three possibilities have been suggested by Michon & Kinoshita (1967) This enzyme may be concerned with cation transport it may represent a rudiment of phylogenetic development, or it may protect the capsule against any acetylcholine in the aqueous or the vitreous

This study was designed to throw further light on the way(s) in which phospholine iodide affects the rabbit lens In addition to pyridine nucleotides major metabolites of the glycolytic pentose phosphate and sorbitol pathways were analyzed in a search for information about the possible causes of the ATP decrease in phospholine treated lenses

Material and Methods

Fifteen adult albino rabbits of the same age were used in the experiments. 0 25 % phospholine iodide drops were instilled twice a day into both eyes of 5 rabbits for 18 weeks Another 5 rabbits were treated in the same way in the right eye only and 5 rabbits served as controls The control rabbits received the same care as the treated rabbits throughout the study The rabbits were killed by injection of air into the auricular vein and the eyeballs were excised The lenses were rapidly removed by the posterior route freed from extraneous tissue and dropped into liquid nitrogen The operation was performed as quickly

as possible and usually not more than 30 second elapsed from the death of the animal *until the lenses were immersed in the liquid nitrogen*

For metabolite studies the material was prepared as described by Harkonen & Tarkkanen (1970) This method provides metabolically *the most active portion* of the lens for study in situations where changes in lens metabolites are to be analyzed The metabolites were measured fluorometrically by enzymatic pyridine nucleotide methods Sorbitol was measured according to Matschinsky & Ellerman (1968) and fructose 1 6 diphosphate according to Lowry et al (1964) by developing the fluorescence of NAD^+ with strong alkali after destroying NADH with acid (see Lowry & Passonneau 1972) 6 Phosphogluconate (Kauffman & Albuquerque 1970) pyruvate and α ketoglutarate (Matschinsky et al 1968) were measured in one tenth of the volume (0 1 ml) of the original procedure *in special microtubes designed* for use in the Farrand fluorometer model A 3

Pyridine nucleotides were determined by a modification of the method of Burch et al (1967) Frozen samples (ca 30 mg) were homogenized at 0 C in 500 μl of 0 04 N NaOH containing 0.5 mM cysteine (NaOH cysteine Total and reduced forms of NAD and NADP were measured in a portion of the homogenate diluted with 20 volumes of cold NADH cysteine NADH and NADPH were measured in a portion of the diluted homogenate in which oxidized pyridine nucleotides had been destroyed by heating for 10 min at 60 C To 200 μl of the original homogenate 5 μl of 1 2 M ascorbic acid was added and the mixture was acidified with 200 μl of 0 02 N H_2SO_4 – 0 1 M Na_2SO_4 and heated for 30 min at 60 C to destroy reduced forms of the nucleotides Oxidized NAD and NADP were then measured Special care was taken to keep samples and standards at 0 C unless *otherwise stated until the cycling step* was started about 40 min after homogenization Cycling was performed in 100 μl of cycling reagent *the rate of* NADP *cycling was ca 8000/h and of* NAD *ca. 2700/h*

Statistical analyses of the results were carried out either by the *t* test according to De Jonge (1964) or by a matched pair *t* test (Richterich 1968) when the eyes of the same rabbits were compared

Results

Normal values

The concentrations of ten metabolites measured in the equatorial region of the rabbit lens are compared with previously reported values in Tables I and II At this point it has to be emphasized that whole lenses were used in the cited papers However the figures give a rough estimate of the quantity of the

Table I

The effect of phospholine iodide (PI) on the concentrations of metabolic intermediates in the rabbit lens (mean ± SEM)

Group	FDP	Pyruvate	a GOP μmol × kg⁻¹	6 PG wet tissue	a kG	Sorbitol
Controls						
Both lenses	9 0 ± 2 5	15 4 ± 2 1	1250 ± 50	11 1 ± 1 0	51 1 ± 2 0	9140 ± 1550
Left lenses	8 7 ± 5 7	13 0 ± 2 7	1200 ± 50	11 3 ± 1 3	52 4 ± 2 7	9270 ± 1480
PI to the right eye						
Left lenses	26 3 ± 5 3*	15 7 ± 5 5	1110 ± 180	20 8 ± 9 4	40 3 ± 6 2	5890 ± 940
Right lenses	27 5 ± 9 3	18 3 ± 5 7	1124 ± 66	17 3 ± 7 5	41 5 ± 8 9	6500 ± 990
PI to both eyes						
Both lenses	26 6 ± 5 7*	24 2 ± 4 4	1070 ± 50 ¹	7 1 ± 0 7 ¹	53 5 ± 3 4	4790 ± 350
Values from other reports	–	60	940	–	–	1700³

van Heyningen (1965)
³ Kuck (1966) 31 mg/100 g
* $P < 0\ 05$
¹ $P < 0\ 0$

Table II

The effect of phospholine iodide (I I) on the concentrations of metabolic intermediates in the rabbit len (mean ± SEM)

Group	Total NAD measured	NAD+	NADH	NAD+/NADH	Total NADP measured	NADP+	NADPH	NADPH/NADP+	Total NAD/Total NADP
			μmol × kg⁻¹ wet tissue						
Controls Both lenses	834 ± 93	3.8 ± 69	469 ± 34	0 74 ± 0 09	32 5 ± 0 8	9? ± 1 6	?8 1 ± 0 8	3 5 ± 0 5	25 5 ± 2 5
I I to the right eye Right lenses	863 ± 76	344 ± 52	504 ± 3?	0 67 ± 0 09	21 5 ± 1 6***	9 9 ± 1 9	15 7 ± 2 0**	1 7 ± 0 1*	39 9 ± 5 6*
I I to both eyes Both lenses	878 ± 6?	414 ± 79	4.6 ± 26	0 93 ± 0 19	22? ± 1 9*	7 3 ± 1 1	19 2 ± 1 2**	2 7 ± 0 2	42 0 ± ? 1
Values from other reports	–	?72[2]	337[2]	1 57	–	120	48	0 40[2]	

[2] Lullard (1965)
* $P < 0 0?$
** $P < 0 01$
*** $P < 0 001$

given metabolites The values for α glycerophosphate pyruvate NAD^+ and NADH agreed rather well with those of van Heyningen (1965) and Bullard (1965) However the concentrations of $NADP^+$ and NADPH were a tenth and a half of the respective concentrations found by Bullard (1965) The NADPH/$NADP^+$ ratio was 3 5 in our study whereas Bullard's values gave the ratio 0 40 In most tissues the NADP system is in reduced state the NADPH/$NADP^+$ ratio varying from 2 8 to 20 6 (see e g Burch et al 1967) In rat and bovine lenses the NADP system is also reported to exist in reduced state (Sippel 1962 Lerman 1961 Klethi & Mandel 1960) In our study the NAD^+/NADH ratio was 0 71 This ratio although higher than in most other tissues is far lower than in several previous studies on rabbit and bovine lenses where the ratio has been shown to be greater than unity (Bullard 1965 Klethi & Mandel 1960) However in the rat lens the ratio has been reported to be either higher (Sippel 1962) or lower (Lerman 1961 Lerman & Heggeness 1961) than unity In our study the total NAD measured agreed within 1 % with the sum of the reduced and oxidized forms whereas the total NADP measured was less than the sum of the oxidized and reduced NADP The sorbitol concentration was near 5 fold higher than previously reported for the rabbit lens (Kuck 1966)

Metabolite concentrations in lenses treated with phospholine iodide

Cataract formation could not be observed in any of the eyes treated with phospholine iodide confirming our previous results (Harkonen & Tarkkanen 1971) The final metabolite concentrations in the various experimental groups are presented in Tables I and II No significant differences were observed in any of the metabolites measured if the drug was applied to one eye the other eye of the same animal serving as a control Fructose diphosphate was significantly ($P < 0.05$) increased in the lenses of the rabbits which had both eyes treated with phospholine iodide as compared with those of the untreated controls The lenses of the untreated (control) left eye in the group in which the right eye was treated with phospholine iodide also had elevated fructose diphosphate values as compared with the lenses of the left eyes of the untreated controls ($P < 0.05$) Phospholine iodide treatment also had a tendency to elevate the pyruvate concentration These differences in fructose diphosphate and pyruvate concentrations indicate increased glycolytic activity (Lowry et al 1964) In the group in which both eyes were treated with phospholine iodide the 6 phosphogluconate concentration was significantly ($P < 0.02$) lower than in the control group Between the other groups however there were no significant differences and the variation in those groups was wide Sorbitol ($P < 0.0?$)

and α glycerophosphate ($P < 0\ 05$) concentrations were also decreased in the drug treated lenses and the control lenses in the group where the opposite eye was treated with the drug tended to be lower than in the control group In α ketoglutarate concentration there were no significant differences between the groups

Concentrations and ratios of oxidized and reduced nicotinamide adenine dinucleotides were not significantly different in drug treated and corresponding control lenses (Table II) In contrast NADPH and total NADP concentrations as well as the NADPH/NADP+ ratio were significantly decreased in the lenses treated with phospholine iodide Hence the total NAD/total NADP ratio was increased by drug treatment

Discussion

In tissue culture in the presence of phospholine iodide the lens gained water and sodium and lost potassium (Michon & Kinoshita 1968a) The basic change was found to be an increase in lens permeability as measured by the leaking out of rubidium 86 from the lens The permeability altered before any gain in water had occurred and even when the lens was prevented from swelling by a hyperosmotic environment (Michon & Kinoshita 1968b) In our previous study (Harkonen & Tarkkanen 1970) ATP was found to be decreased by 35 % and lactate by 17 % in rabbit lenses after topical phospholine iodide instillation for 15 weeks Only an enhanced rate of glycolysis would have maintained a normal ATP level in the lens as the importance of the citric acid cycle in the lens is still a matter of dispute (Kuck 1970)

Comparison of glycolytic intermediates and the total NAD/total NADP ratios in lenses treated with phospholine iodide and in controls suggested that the treatment increased glycolysis (Lowry et al 1964) In our previous paper we found a decrease of lactate concentration in lenses treated with phospholine iodide (Harkonen & Tarkkanen 1970) This was assumed to be due to inhibition of glycolysis by phospholine iodide However the decrease in lactate concentration in the lens could also be explained by the direct effect of phospholine iodide on lens permeability Even though glycolysis was enhanced the lactate concentration did not rise because the lactate generated could escape through the epithelial cell membrane more easily than in an intact lens

The function of the sorbitol pathway in the lens remains an enigma although there is no lack of theories (Kuck 1970) Kuck (1961) suggested that these enzymes act as a pyridine nucleotide transhydrogenase system taking up the hydrogen removed from the glucose molecule by the first two steps of the

pentose phosphate pathway and converting it into a form which can be used for the production of energy In most tissues the role of the pentose phosphate pathway is to synthesize nucleic acids and fatty acids by producing a carbon skeleton and reducing equivalents In the lens however it is doubtful whether this pathway has the same function because there is little need of material for rapid cell growth or fatty acid synthesis The oxidative portion of the pathway has been shown to be present in the lens but the other steps have not been demonstrated convincingly and glucose metabolism via this pathway in the lens accounts for only a small proportion of the total glucose used Glucose 6 phosphate dehydrogenase is assumed to be the regulatory enzyme of the pathway (see e g Kauffman & Albuquerque 1970 Lowry & Passonneau 1969) Therefore the decrease of 6 phosphogluconate NADPH total NADP and sorbitol concentrations in lenses treated with phospholine iodide could be attributed to the decreased activities of the pentose phosphate and sorbitol pathways This would leave more glucose 6 phosphate for glycolysis

The high concentration of α glycerophosphate suggested that this intermediate might play some role in the energy metabolism of the lens Most of it originates from reduction of dihydroxyacetone phosphate by NADH and its further metabolism is much slower than its production (Kuck 1970) Since mitochondria are confined almost exclusively to the lens epithelium (see van Heyningen 1970) the functioning of the α glycerophosphate shuttle in lens metabolism must be limited to the epithelium The observed decrease in the α glycerophosphate concentration of lenses treated with phospholine iodide could be interpreted as a result of diminished flux into the shuttle at α glycerophosphate dehydrogenase because of enhanced glycolysis

We also investigated the possible acute effects of phospholine iodide in the following way The rabbits were given 2 drops of 0 25 % phospholine iodide to both eyes and enucleation was performed 4 5 hours later when maximum local effects had been obtained The ATP levels in the treated lenses (1 41 ± 0 23 mmol/kg) showed some decrease as compared to the control values (1 90 ± 0 20 mmol/kg) A similar decreasing tendency was observed in the fructose diphosphate α glycerophosphate and glucose 6 phosphate concentrations whereas the dihydroxyacetone phosphate 6 phosphogluconate sorbitol and pyruvate levels after phospholine iodide treatment were of the same magnitude as those of the controls Even though this data is of a very preliminary nature it may be taken as indicating that phospholine iodide interferes with lens metabolism immediately after instillation although the more pronounced metabolic changes are apparent following long term application

Michon & Kinoshita (1968b) reported that in tissue culture demecarium bromide shifted lens metabolism to anaerobic pathways whereas phospholine

iodide had no effect The concentrations of these drugs required to alter the normal state of the lens were so high that such levels would never be reached in clinical situations Therefore the authors concluded that these drugs probably *do no harm in the patient situation* However our data suggest that long term phospholine iodide treatment in therapeutic concentrations does interfere with the energy metabolism of the lens The increased demand for ATP is met by enhanced glycolytic activity whereas the other metabolic pathways are suppressed *The primary cause of the change in lens permeability* induced by phospholine iodide still remains obscure It is well known that locally instilled anticholinesterase agents can depress the serum and red blood cell cholinesterase activities and also that the locally to the eye applied drug can readily penetrate *the placental barrier* (Birks et al 1969) *Therefore one cannot exclude a systemic* effect as a source of the ocular changes The data show however that the response of a tissue to certain drugs *in vitro* and *in vivo* may be different and that results obtained *in vitro* cannot always be extended to apply to *in vivo* conditions *Therefore caution should be exercised in long term treatment of* patients with phospholine iodide.

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THE CYCLOPENTOLATE PROVOCATIVE TEST IN SUSPECTED OR UNTREATED OPEN ANGLE GLAUCOMA

I Effect on Intraocular Pressure

BY

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The mydriasis provocative test with 1 % cyclopentolate (CPT) was performed on 218 patients with suspected or untreated open angle glaucoma on 431 eyes in all Gonioscopy was performed before and during the test to ensure that te chamber angles were open throughout The effect of cyclopentolate on intraocular pressure (IOP) in these eyes is reported in the present paper

The mean change in IOP (± SD) during CPT was +2 5 ± 3 1 mmHg in the glaucoma group (196 eyes) +0 4 ± 2 5 mmHg in the group with suspicion of open angle glaucoma (235 eyes) and +1 4 ± 2 9 mmHg in the total series The difference in IOP change between the groups with glaucoma and su pected glaucoma is statistically highly significant

The incidence of positive responses (IOP rise ≧ 8 mmHg) in the glaucoma group (8 7 % 17 eyes) was significantly higher than in the suspicion group (1 7 % 4 eyes) Significant IOP elevations in the total series were demonstrated in 21 eyes of 18 patients (4 9 %) Including the borderline cases IOP elevations ≧ 5 mmHg were also significantly more frequent in eyes with glaucoma (24 0 % 47 eyes) than in eyes with suspected glaucoma (11 9 % 28 eyes)

The occurrence and magnitude of positive responses were not dependent on the initial IOP level Further analysis of the responder group and clinical studies of the mechanism of IOP elevation on the same patients are presented in parts II and III

Key words cyclopentolate – intraocular pressure – mydriasis provocative test – open angle glaucoma – suspicion of open angle glaucoma

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The mydriasis provocative test (MPT) is a commonly used test in the diagnostics of *narrow angle* glaucoma Mydriasis may cause further narrowing of an initially narrow chamber angle or its closure with the base of the iris pressing against the trabecular zone so that the aqueous outflow is obstructed or inhibited and rapid elevation of intraocular pressure (IOP) follows

Marked elevations of IOP in connection with mydriasis have been encountered also in eyes with definitely open chamber angles Gonioscopy has been performed on these eyes before and during MPT to ensure that the chamber angles are open throughout This excludes mechanical obstruction of the angle during the test as a cause of the IOP elevation These patients constitute an interesting group Why does IOP rise distinctly in them during mydriasis *although the chamber angles are open throughout*? The answer to this question remains open even though there are in the literature numerous studies and observations of the effect of mydriatics and cycloplegics on IOP in open angle eyes – the procedure in question is in fact a very common and simple measure However the materials have generally been small and the problem has been inadequately investigated

Healthy subjects without glaucoma and with open chamber angles revealed a small mean change in IOP ranging from −0 5 mmHg (Christensen & Pearce 1963) to +1 5 mmHg (Makabe 1970b) with different parasympatholytics Occasionally parasympatholytics in healthy eyes might cause distinct IOP elevations (Leydhecker 1954 Galin 1961 Harris 1968) though even then generally only 6–8 mmHg According to Kronfeld et al (1943) Christensen & Pearce (1963) and Makabe (1965 1970a b) parasympatholytics did not provoke marked IOP elevations in healthy subjects Sympathomimetics have not been observed to provoke even occasionally distinct IOP elevations in healthy eyes (Lee 1958 Becker et al 1959 Kristensen 1965)

In *patients with simple glaucoma* parasympatholytics topically used raise the mean IOP The means range between +1 0 mmHg (Sugar 1948) and +5 6 mmHg (Kronfeld et al 1943) Sympathomimetics on the other hand have been found to cause a moderate mean decrease in the IOP of patients with simple glaucoma Sugar (1948) observed a mean decrease of −1 5 mmHg in IOP after MPT with 10 % phenylephrine hydrochloride (10 % Neosynephrine®) Becker et al (1959) one of −1 9 mmHg and Kristensen (1965) also reported a slight fall in most of his patients

Observations of marked IOP elevations provoked by parasympatholytics and sympathomimetics in open angle glaucoma patients vary greatly

Several authors have detected no distinct IOP elevations in *provocative tests* with *sympathomimetics* (Bloomfield & Kellerman 1947 Schimek & Lieberman 1961 Harris 1968) Some instances of distinct IOP elevations due to the use

of sympathomimetics on open angle glaucoma patients have been reported by e g (Kronfeld et al 1943 Sugar 1948 Leydhecker 1951 Lee 1958 Katavisto 1964 Kristensen 1965 Haddad et al 1970) Using 10 % Neosynephrine® on patients with simple glaucoma Hill (1968) observed a rise of 6–23 mmHg in IOP in 20 % and Kristensen (1968) reported an elevation ≥ 8 mmHg after two hours in as high a percentage as 48 4 after epitromin and 10 % meta oxedrin provocation The average IOP elevation was 8 2 mmHg the maximal rise was 28 mmHg and the maximal fall 10 mmHg In all the eyes there was also liberation of pigment into the aqueous sometimes very profuse during the test.

Marked IOP elevations were observed by Leydhecker (1951 1954 1955) in 6–14 5 % of different materials after the administration of *parasympatholytics* Several other authors have reported distinct IOP elevations in eyes with simple glaucoma following the topical use of various parasympatholytics (Kollner 1921 Streiff 1937 Teraskeli 1939 Kronfeld et al 1943 Galin 1961 Christensen & Pearce 1963 Smeral et al 1964 Lazenby et al 1968) The materials were small Sugar (1948) observed not a single rise in IOP in 51 open angle glaucoma eyes an hour after the instillation of 4 % homatropine According to Leydhecker (1951) an IOP elevation of ad 12 mmHg may be caused solely by the vascular action of the mydriatic or cycloplegic drug The IOP rises after about 45 min and remains at a steadily elevated level for the duration of the drug action

Concurrent miotic therapy distinctly increased the incidence of marked IOP elevations during the mydriasis provocative test (MPT) (Harris & Galin 1969) They instilled 1 % cyclopentolate in one eye of 69 open angle glaucoma patients under miotic therapy and observed an IOP elevation ≥ 6 mmHg after 1–1½ h in 43 % of them When the same patients had no miotic therapy for two weeks and the cyclopentolate provocative test (CPT) was repeated 24 % displayed a distinct rise in IOP i e a positive response The miotic therapy did not affect the magnitude of the response According to the authors cycloplegic blocks the tension lowering action of the miotic in approx 50 % of the responders under miotic therapy In the other cases direct action of the cycloplegic on the ciliary muscle is possibly involved (Harris 1968 Harris & Galin 1969) Schimek & Lieberman (1961) established an elevation ≥ 8 mmHg with 1 % cyclopentolate in nine of 17 eyes under miotic therapy and observed at the same time in all of them a distinct weakening of aqueous outflow facility

Performing the MPT on new previously untreated or suspected cases of open angle glaucoma is especially interesting as regards the occurrence of positive responses The potential role of earlier chemotherapy of glaucoma on intraocular pressure changes and/or on the aqueous dynamics is ruled out in these patients

In this study MPT was performed with 1 % cyclopentolate on new previously untreated or suspected cases of open angle glaucoma The purpose was to elucidate from a sufficiently comprehensive material the incidence of significant IOP elevations and the average change in IOP during the CPT in this group of patients The same patients also underwent other glaucoma investigations and the responders and non responders were also compared for other criteria of glaucoma An endeavour was made to find out whether it is possible by means of CPT to distinguish a group of eyes or patients which differ perhaps even in some other respect from other open angle glaucoma eyes or patients *Furthermore additional information was sought on the mechanism of IOP* elevation in responders

The present paper is confined to a study of the effect of CPT on IOP in the patients of the material Other analyses of the series and clinical studies on the mechanism of IOP elevation in responders are presented in parts II and III

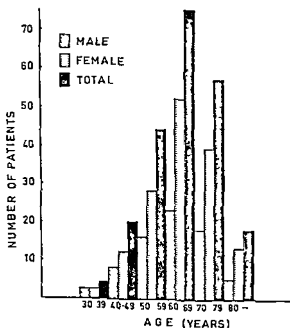


Fig 1
Age and sex distribution of the 218 patients in the material

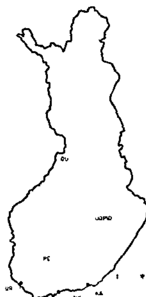


Fig 2

Location of the Central Hospital District of Kotka (dotted area) on the map of Finland The five university cities with a Faculty of Medicine are also shown

Material and Methods

The material consisted of 218 patients with a new previously untreated or suspected open angle glaucoma 431 eyes in all There were 72 men and 146 women Their mean age was 64 9 ± 8 7 years The youngest was a man aged 33 the oldest a woman of 91 years The age and sex distribution of the patients is given in Fig 1

All the patients in series were from the region of the Central Hospital District of Kotka (Fig 2) the population of which on December 31 1972 was 194 919 77 430 (39 7 %) were over 40 34 198 (44 2 %) of them men and 43 232 (55 8 %) women (Central Statistical Office of Finland Tilastotiedotus Va 1974 24 pp 6 37–42) According to a publication (T 6 6 Helsinki 1973) of the Statistical Office of the Social Insurance Institution 5186 men and 11 715 women in all 16 901 persons in Finland received on June 30 1973 full compensation for glaucoma chemotherapy In all 687 persons – 213 men and 474 women – of these were resident in the region of the Central Hospital District of Kotka representing 0 9 % of the population aged over 40 years

All the patients in the series attended the Department of Ophthalmology Central Hospital of Kotka which is the only ophthalmological department in the district, for diagnostic studies in 1968–19[illegible] The diagnosis and treatment of glaucoma patients within the district is centralised in this department The aim has been to admit every new or suspected case of glaucoma to this hospital for diagnostic investigations and if necessary the institution of therapy The six ophthalmologists working within the

district (including the three ophthalmologists of the hospital) referred the patients to the Department of Ophthalmology after diagnosing new previously untreated or suspected glaucoma either in their private practice or at the out patient department The criterion for suspicion of glaucoma was elevated IOP (≥ 25 mmHg) measured once or several times in one or both eyes In addition suspicion of open angle glaucoma was corroborated by manifest or suspected cupping of the optic disc the presence of pseudoexfoliation or a *family history of glaucoma To avoid unnecessarily* many admissions of patients who had only intraocular hypertension without glaucoma the ophthalmologists of the district have been able to refer their patients for investigation of visual fields and tonography on an out patient basis Thorough examination for glaucoma at the ward was indicated when visual field defects were demonstrated or when the tonographic values were pathological or suspicious (Table I)

The author personally examined and performed the CPT on all the patients It *was of essential importance to make sure with gonioscopy that the chamber angles* were definitely open throughout the study Patients with even slightly narrowed chamber angles were excluded from the material Gonioscopy was repeated during CPT if a distinct rise in IOP was observed to ensure that the chamber angles were open also during CPT

All the patients of the series were examined in accordance with the same 3 day glaucoma investigation programme performed in the same order

1st day Basic examination visual acuity lenses pseudoexfoliation + ++ +++ or − optic discs applanation tonometry and Schiotz tonometry using three different weights to elicit possible rigidity abnormalities Gonioscopy in which attention was *paid to the degree of patency of the chamber angle and the grade of pigmentation.* 4 min tonography (V Mueller) visual fields (Goldmann) diurnal tension curve (12 15 18 2? 6 9 h)

nd day *Water drinking test (beginning at 08 30 h)* with applanation tonometry before and 90 min after the drinking of 1 litre of fluid. Diurnal tension curve continued between 1? 00 and 16 00 at hourly intervals.

Table 1

Classification of values used in this study for the diagnosis of open angle glaucoma in eyes showing open angles and elevated intraocular pressures in the absence of field loss and cupping (after Tarkkanen 1962)

Test	Normal	Suspect	Glaucoma
Intraocular pressure (mmHg)	≤ 21	22–24	≥ 25
Outflow facility	≥ 0 19	0 18–0 13	≤ 0 1
P /C	< 100	100– 00	> 200
Increase of intraocular pressure after water drinking (mmHg)	≤ 6	–9	≥ 10
Diurnal variations (mmHg)	≤ 3	4–5	≥ 6

3rd day Diurnal tension curve continued (6 9 12 13 16 18 22 6 h) The *cyclopentolate provocative test* (CPT) was begun at 13 00 h as follows Measurement of IOP with both Schiotz and applanation tonometer and biomicroscopy (Haag Streit 900) for examination of the clarity of the aqueous One drop of 1 % cyclopentolate (1 % of Oftan Syklo® Star) was instilled twice with a 15 min interval into both eyes The patients were not allowed food drink tobacco or other drugs for three h during the test and for two h before it Intraocular pressures were measured with a Schiotz tonometer at 30 min intervals for three h If the IOP was then still clearly (≳ 5 mmHg) higher than the initial level the measurements were continued for some hours at 60 min intervals Sixty min after the beginning of the test applanation tonometry and biomicroscopy were repeated The possible liberation of pigment into the aqueous during CPT and its quantitative amount (pigment liberation test PLT) were recorded using the grading system 0–6 introduced by Mitsui (1943 1961) If IOP rose significantly (≧ 5 mmHg) a new gonioscopy was performed to ensure that the chamber angle was still mechanically open. When the CPT was positive (rise of IOP ≧ 8 mmHg) applanation tonometry and control of pigment liberation into the aqueous were continued for some hours at hourly intervals The local anaesthetic for tonometry was 0 4 % oxibuprocaine (Ocu Novesin® Orion Wander)

Tonography during CPT tonography was performed 1½–2 h after the beginning of CPT The tonography values recorded were thus comparable with those taken from the same patients at the same hour two days earlier

Gonioscopy was performed with Goldmann s gonioscopy lens Applying the gonioscopy classification introduced by Corin & Iosner (1968) only wide angle eyes with the whole trabecular zone and a part of the ciliary body visible were included in the material This excludes a narrow angle mechanism Intermediate angle and narrow angle eyes were excluded from the material

The degree of pigmentation in the chamber angle was divided into four grades I–IV according to Tarkkanen (1962)

Details concerning the tonographic study were reported in a previous publication (Valle 1974) dealing with the effect of cyclopentolate on the aqueous dynamics in the same patients

Criteria of open angle glaucoma

Variations up to two standard deviations or less from the normal mean were considered normal those within two and three standard deviations as suspect and the ones above three standard deviations as glaucomatous According to the normal Gaussian distribution 2 27 % of normal eyes belong thus to the suspect group and 0 13 % to the glaucoma group (Leydhecker & Niesel 1954 Tarkkanen 1962)

The criteria of open angle glaucoma used in this study are presented in Table I In eyes with normal optic discs and visual fields diagnosis of open angle glaucoma was made when in addition to elevated IOP (≧ 25 mmHg measured at least twice) at least one pathological criterion was met from the glaucoma column The diagnosis of open angle glaucoma was clear in eyes showing a typical field loss and cupping

Diagnosis of chronic capsular glaucoma required in addition to open angle glaucoma also pseudoexfoliation of the anterior lens capsule Chronic pigmentary glaucoma required in this study in addition to open angle glaucoma also myopia massive pig

Table II

Studies reported in the literature on the effect of the mydriasis provocative test on IOP in healthy eyes with open angles

Author	Year	Cycloplegic drug topically used	No of eyes	Change in IOP (mmHg) (M ± SD)	Pathological value limit (mmHg) (rounded)	
					M + 2 SD	M + 3 SD
Leydhecker	1954	homatropine 1 %	120	−0 2 ± 3 6	7	11*
Harris	1968	cyclopentolate 1 %	100	+0 5 ?	**	**
Groeschel & Rast	1970	cyclopentolate 0 5 %	109	+0 4 ± 2 0	5	7
Makabe	1970a	tropicamide 0 5 %	84	+1 3 ± 2 1	6	8

* 99 % pathological limit 8 mmHg

** The author gives 6 mmHg as the limit of the pathological response

mentation (Grade IV) in the ciliary body chamber angle and the posterior surface of the marginal parts of the cornea and Krukenberg's spindle Patients with chronic simple capsular and pigmentary glaucoma were grouped together as cases of open angle glaucoma here

There are fairly few studies in which MFT was performed on healthy eyes with open angles and the results were analysed statistically The cycloplegic drug used was also different in all the studies Investigations of this type are assembled in Table II The present material was divided into the following groups on the basis of the response to cyclopentolate and in accordance with the results presented in Table II

Responders positive cyclopentolate response elevation of IOP ≥ 8 mmHg

Borderline cases elevation of IOP 5–7 mmHg

Non responders negative cyclopentolate response elevation of IOP ≤ 4 mmHg or fall in IOP

The material was divided into two groups by the results of the glaucoma investigations Group I eyes in which a new previously untreated open angle glaucoma was found Group II eyes with suspicion of open angle glaucoma in which no glaucoma was established on the basis of the criteria applied This group includes also the fellow eyes of patients with unilateral glaucoma or suspicion of glaucoma most of which were normal

Student's *t* test and the chi square tests were used for the statistical analysis of the results

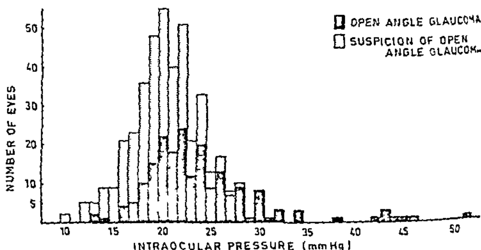


Fig 3

Distribution of the intraocular pressures of 431 eyes at the beginning of the cyclopentolate provocative test

mentation (Grade IV) in the ciliary body chamber angle and the posterior surface of the marginal parts of the cornea and Krukenberg's spindle. Patients with chronic simple capsular and pigmentary glaucoma were grouped together as cases of open angle glaucoma here.

There are fairly few studies in which MPT was performed on healthy eyes with open angles and the results were analysed statistically. The cycloplegic drug used was also different in all the studies. Investigations of this type are assembled in Table II. The present material was divided into the following groups on the basis of the response to cyclopentolate and in accordance with the results presented in Table II.

Responders: positive cyclopentolate response, elevation of IOP ≥ 8 mmHg.

Borderline cases: elevation of IOP 5–7 mmHg.

Non-responders: negative cyclopentolate response, elevation of IOP ≤ 4 mmHg or fall in IOP.

The material was divided into two groups by the results of the glaucoma investigations. Group I: eyes in which a new, previously untreated open angle glaucoma was found. Group II: eyes with suspicion of open angle glaucoma in which no glaucoma was established on the basis of the criteria applied. This group includes also the fellow eyes of patients with unilateral glaucoma or suspicion of glaucoma, most of which were normal.

Student's *t* test and the chi square tests were used for the statistical analysis of the results.

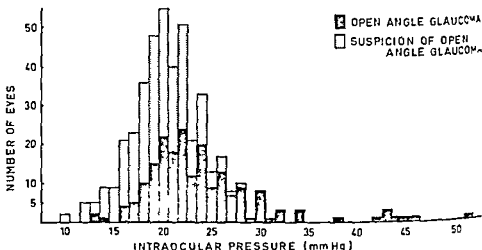


Fig. 3

Distribution of the intraocular pressures of 431 eyes at the beginning of the cyclopentolate provocative test

Table IV

Elevation of IOP during the cyclopentolate provocative test (CPT) in the 218 patients of the series Group I glaucoma group patients with recently diagnosed open angle glaucoma Group II suspicion group patients in whom open angle glaucoma was suspected but was not established at investigations

	Result of the CPT (change in IOP)					
	Group I		Group II		Total	
	No	%	No	%	No	%
*Positive (≥ 8 mmHg)	15	13.1	3	2.9	18	8.3
*Borderline (5–7 mmHg)	24	21.1	14	13.5	38	17.4
Negative (≤ 4 mmHg)	75	65.8	87	83.6	162	74.3
No of patients	114	100.0	104	100.0	218	100.0

* Elevation of IOP in one or both eyes

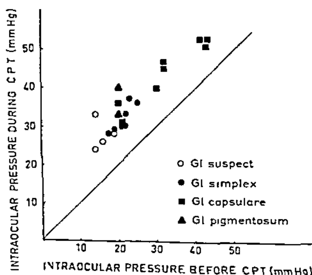


Fig 5

Distribution of intraocular pressures before and during the cyclopentolate provocative test (CPT) in 91 eyes with a positive cyclopentolate response

Table III

Elevation of IOP during the cyclopentolate provocative test (CPT) in the 431 eyes of the series analysed individually Group I glaucoma group eyes with recently diagnosed *open angle glaucoma* *Group II suspicion group eyes in which open angle* glaucoma was suspected but was not established at investigations

	Result of the CPT (change in IOP)					
	Group I		Group II		Total	
	No	%	No	%	No	%
Positive ($\geq$ 8 mmHg)	17	8 7	4	1 7	21	4 9
Borderline (5–7 mmHg)	30	15 3	24	10 2	54	12 5
Negative ($\leq$ 4 mmHg)	149	76 0	207	88 1	356	82 6
No of eyes	196	100 0	235	100 0	431	100 0

mean change in IOP was +0 4 ± 2 5 mmHg The maximal changes were +19 mmHg and –8 mmHg The mean difference in the IOP change between the glaucoma group and the suspicion group is statistically highly significant ($P < 0\ 001$)

Incidence of significant IOP elevations

Table III shows the maximal elevation of IOP during CPT in 431 eyes of the series grouped by the response

A positive response (*rise of IOP* $\geq$ *8 mmHg*) during CPT was demonstrated in 17 (8 7 %) of the eyes of the glaucoma group in 4 (1 7 %) of the eyes of the suspicion group and in the total series in 4 9 % 21 eyes in all The difference in the incidence of positive responses between the glaucoma and suspicion groups is statistically significant ($P < 0\ 01$) Borderline responders accounted for 30 (15 3 %) of the glaucomatous eyes 24 (10 2 %) of the eyes with suspected glaucoma and 54 (12 5 %) of the total series An IOP elevation $\geq$ 5 mmHg during CPT was established in 47 (24 0 %) of the eyes with glaucoma in 28 (11 9 %) of the eyes with suspicion of glaucoma The difference between the groups is statistically significant ($P < 0\ 01$)

Table IV

Elevation of IOP during the cyclopentolate provocative test (CPT) in the 218 patients of the series Group I glaucoma group patients with recently diagnosed open angle glaucoma Group II suspicion group patients in whom open angle glaucoma was suspected but was not established at investigations

	Result of the CPT (change in IOP)					
	Group I		Group II		Total	
	No	%	No	%	No	%
Positive (≧ 8 mmHg)	15	13 1	3	2 9	18	8.3
*Borderline (5–7 mmHg)	24	21 1	14	13 5	38	17 4
Negative (≦ 4 mmHg)	75	65 8	87	83 6	162	74 3
No of patients	114	100 0	104	100 0	218	100 0

* Elevation of IOP in one or both eyes

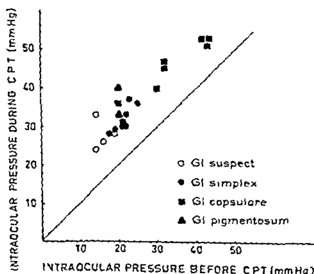


Fig 5

Distribution of intraocular pressures before and during the cyclopentolate provocative test (CPT) in 21 eyes with a positive cyclopentolate response

in 1–3 h in only four eyes more slowly not until 5–6 h from the beginning of CPT (Fig 6) When the response appeared the IOP generally remained fairly steadily elevated for 1–2 h Observation for 5–6 h including tonometry is laborious in itself and the reliability of the result also decreases as many other factors in addition to the mydriatic or cycloplegic influence the IOP (e g spontaneous IOP variations eating drinking smoking other drugs) On the strength of the experience gained here an observation time of three hours with IOP measured 1–3 h after the beginning of the test at either 30- or 60 min intervals seems to be sufficient in general Tonography performed during MPT increases the reliability of the test and improves its diagnostic value (Smeral et al 1964 Makabe 1968)

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of IOP in the 48 h tension curve the occurrence of cupping of the optic disc or visual field defects between the responder and non responder eyes in the glaucomatous group

Key words cyclopentolate – intraocular pressure – mydriasis provocative test – open angle glaucoma – pseudoexfoliation – suspicion of open angle glaucoma

Distinct elevations of intraocular pressure (IOP) have been established after the administration of both parasympatholytic and sympathomimetic mydriatics in open angle eyes in which the narrowing or closure of the chamber angle has been ruled out gonioscopically These marked IOP elevations or responses have been demonstrated in both treated and new previously untreated open angle glaucoma eyes with parasympatholytics incidentally also in eyes without glaucoma (references see Part I Valle 1976)

The IOP elevations have been associated with changes in the aqueous dynamics during the mydriasis provocative test (MPT) when the aqueous outflow facility (outflow) is impaired (Lee 1958 Galin 1961 Schimek & Lieberman 1961 Christensen & Pearce 1963 Smeral et al 1964 Barany & Christensen 1967 Iwata et al 1968 Kristensen 1968 Makabe 1968 1969a b 1970 Valle 1974) A significant difference between the responder and non responder eyes has been observed concurrently in the changes in aqueous inflow which explains the significant IOP elevation demonstrated in the responder eyes (Valle 1974)

The exact mechanism of IOP elevation is insufficiently known The parasympatholytic or sympathomimetic drug used in MPT causes e g the following mechanisms of action

1 Dilates the pupil i e mydriatic effect 2 Affects the vasculature 3 Affects the tonus of the ciliary muscle 4 Affects the width and shape of the chamber angle 5 Affects the aqueous dynamics

The pupillary diameter during MPT has not been observed to be correlated with the elevation of IOP in open angle eyes (Leydhecker 1951 Christensen & Pearce 1963 Harris 1968 Harris & Galin 1969)

Parasympatholytics paralyse the tonus of the ciliary muscle and cause cycloplegia and accommodation paresis 1 % cyclopentolate is a very potent and fast acting cycloplegic stronger than e g 5 % homatropine (Priestley & Medine 1951 Milder & Riffenburgh 1953 Havener 1966) Cyclopentolate is in extensive clinical use both as a cycloplegic for the examination of refraction and as a mydriatic for examination of the fundus of the eye or preoperatively before cataract surgery

According to Leydhecker (1951) an IOP elevation of ad 12 mmHg may be due solely to the vascular action of the drug employed in MPT IOP then rises in approx 45 min and remains evenly elevated through the drug action He found 1 % homatropine provocation to cause an exceptionally pronounced elevation of IOP in both eyes (24 and 34 mmHg) of a patient with open angle glaucoma However the chamber angles were widely open also during the rise in IOP Spontaneous short term fluctuations in IOP were proffered as an explanation (Leydhecker 1954) It is assumed that the paresis of the ciliary muscle causes an increased blood flow into the ciliary body the blood outflow diminishes and the narrowing of the trabeculae and Schlemm s canal result in a decreased aqueous outflow and elevation of IOP (Leydhecker 1954)

It was regarded as obvious already earlier by Fortin (1929a b 1931) and Hruby (1940 1941) that the ciliary muscle regulates also intraocular pressure Harris (1968) observed a causal relationship between IOP elevation induced by 1 % cyclopentolate and accommodation paresis Drugs which have a minimal effect on accommodation did not cause IOP elevation in the same eyes Potent cycloplegics probably have a direct action on the ciliary muscle (Harris & Galin 1969) It has been shown also tonographically that accommodation improves the aqueous outflow (Armaly & Burian 1958)

The present paper is a part of a project to study the effect of 1 % cyclo pentolate on intraocular pressure in patients with suspected or new previously untreated open angle glaucoma Part I (Valle 1976) introduced the investigation project as a whole the material methods criteria and results of the effect of the cyclopentolate provocative test (CPT) on IOP in these patients Special interest was devoted to eyes in which significant IOP elevations i e responses were observed during CPT Part II analyses particularly the responder group and presents other investigation results and clinical findings to obtain additional information on the mechanism of IOP elevation in responders

The results of the effect of cyclopentolate on the aqueous dynamics in the same patients were reported in a previous work (Valle 1974)

Material Methods and Criteria

The patients and the methods and criteria employed in the study were the same as those described in detail in Part I (Valle 1976)

The following criteria and definitions were also used

Pseudoexfoliation (PE) – no PE + mild PE on the surface of the anterior lens capsule and or on the pupillary margin ++ profuse PE central disc and or peripheral band +++ very profuse PE of both central disc and peripheral band type

Lens 0 no cataract + incipient ++ immature +++ mature or feremature cataract.

Optic disc 0 normal + flat cupping of the optic disc to the temporal margin or deep central cupping ++ temporally marginal deep cupping +++ total cupping

Visual field 0 normal + enlarged blind spot incipient Bjerrum s scotoma ++ opened Bjerrum s scotoma and/or nasal step or even more extensive defect +++ central or temporal remnant or total loss

Student s *t* test and the chi square tests were used for the statistical analysis of the results

Results

ANALYSIS OF THE RESPONDER GROUP

Age and sex

Eighteen (8 3 %) of the 218 patients in the total series gave a positive response during CPT (rise of IOP $\geq$ 8 mmHg) in either one or both eyes (Table IV Part I Valle 1976) The age and sex distribution of the responder group is given in Fig 1 The mean age of these patients at the time of investigation was 62 3 ± 10 6 years The mean age of the responders was somewhat lower than that of the total material (64 9 ± 8 7 years) The youngest patient was a man aged 33 and the oldest a man of 80 years

Ten of the responders were women and eight men The responders did not differ from the other patients of the series in age or sex

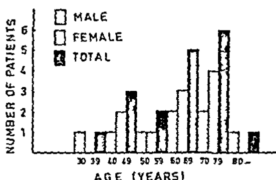


Fig 1
Age and sex distribution of the 18 patients with a positive cyclopentolate response

Table I

The 21 eyes giving a positive response in the cyclopentolate provocative test were distributed into the following diagnostic groups

Chronic capsular glaucoma	8 eyes	8 patients
Suspicion of chronic capsular glaucoma	2 eyes	2 patients
Chronic simple glaucoma	7 eyes	6 patients
Suspicion of chronic simple glaucoma	2 eyes	2 patients
Chronic pigmentary glaucoma	2 eyes	patient
Total	21 eyes	18 patients

* These eyes later developed glaucoma

Diagnostic groups

The eyes with a positive cyclopentolate response were distributed into the following diagnostic groups (Table I)

Occurrence and significance of pseudoexfoliation (PE)

Patients with capsular glaucoma constituted the biggest group (50 %) among the responders nine patients whose mean age was 68 3 ± 4 6 years All the responders in this group were over 60 The material comprised in all 93 PE eyes bilateral 33 unilateral 27 total 60 patients Their mean age was 70 0 ± 6 6 years The youngest was a woman of 49 the oldest a woman aged 87 Only five of the PE patients in the series were under 60 years of age

The responders of the PE group did not differ significantly from the non responders of the group in age

The degree of pseudoexfoliation in the capsular glaucoma responders was profuse in most of the cases (++ six eyes) or very profuse (+++ two eyes) being of lesser degree in the other cases (+ two eyes) Three responders were found to have PE and glaucoma bilaterally However CPT was positive (IOP elevations of 8 11 and 13 mmHg) in only one eye of these cases and in all of them in the eye with more profuse PE Slight IOP elevation (4 5 and 6 mmHg) during CPT was demonstrated also in the fellow eyes in which PE was of lesser degree in these patients One patient with bilateral PE gave a positive response to CPT in both eyes (IOP elevations of 10 and 16 mmHg) Glaucoma was diagnosed in only one eye initially but it developed in the course of nine months also in the fellow eye in which PE and elevation of IOP during CPT were milder originally

Three patients with a positive CPT response in one eye (10, 10 and 15 mmHg elevation in IOP) displayed PE unilaterally and the CPT was positive particularly in the PE eyes. The same eyes also revealed fairly severe capsular glaucoma unilaterally. Elevation of IOP in the fellow eyes was slight (0, 2 and 5 mmHg). Two of the fellow eyes were healthy and one was a borderline case of glaucoma (Table VIII, Nos 19, 20 and 21). The situation has not changed essentially regarding the fellow eyes during the observation period of three to five years.

The series included no contrary cases yielding a positive CPT result in the PE negative eye in patients with unilateral PE. Eyes with PE displayed a positive cyclopentolate response more frequently than eyes without PE – the more distinctly the more profuse the pseudoexfoliation was. This is seen also in Table II.

Table II

Occurrence of pseudoexfoliation and change in IOP during the cyclopentolate provocative test in the different groups of 451 eyes. Group I: eyes with recently diagnosed open angle glaucoma. Group II: eyes suspected of having open angle glaucoma. CR +: responders, positive cyclopentolate response, rise of IOP ≥ 8 mmHg. CR ±: borderline rise of IOP 5–7 mmHg. CR –: non responders, negative cyclopentolate response, rise of IOP ≤ 4 mmHg.

		With pseudoexfoliation (+ ++ +++)	%	Without pseudoexfoliation	%	No of eyes	%
Group I	CR +	8	13.6	9	6.6	17	8.7
	CR ±	10	16.9	[illegible]	14.6	30	15.3
	CR –	41	69.5	108	78.8	149	76.0
	No	59	100.0	137	100.0	196	100.0
Group II	CR +	2*	5.9	2	1.0	4	1.6
	CR ±	0	0.0	24	11.9	24	10.2
	CR –	32	94.1	175	87.1	207	88.1
	No	34	100.0	201	100.0	235	100.0
Total	CR +	10	10.8	11	3.3	21	4.9
	CR ±	10	10.8	44	13.0	54	12.5
	CR –	73*	78.4	283**	83.7	356	82.6
	No	93	100.0	338	100.0	451	100.0

* These eyes later developed glaucoma

** The difference is significant at $P < 0.01$

Table III

Results of the water drinking test in the different groups of the material and correlation with the results of the cyclopentolate provocative test (CPT) on the same patients. Applanation tonometry was performed before and 90 min after drinking 1 litre of water. Group I: eyes with recently diagnosed open angle glaucoma. Group II: eyes suspected of having open angle glaucoma. Responders: positive cyclopentolate response: rise of IOP ≥ 8 mmHg. Non responders + borderline: rise of IOP during CPT ≤ 7 mmHg

Water drinking test	Cyclopentolate provocative test					
	Responders		Non responders + borderline			
			Group I		Group II	
	No	%	No	%	No	%
Positive (≥ 10 mmHg)	4	19.1	26	14.5	9	3.9
Borderline cases (7–9 mmHg)	5	23.8	55	30.7	37	16.0
Negative (≤ 6 mmHg)	10	47.6	98	54.8	181	78.4
Not performed/ failed	2	9.5	0	0	4	1.7
Total (eyes)	21	100.0	179	100.0	231	100.0

The difference between the groups is not significant ($P > 0.05$)

Water drinking test in the patients of the series

The results of the water drinking test in the different groups of the material and the correlation between the results of CPT for the same patients are presented in Table III.

Both tests were positive in the same eye in only four eyes of the total series (431 eyes). The water drinking test on the cyclopentolate responders was negative in 10 out of 19 eyes, borderline in five and positive in no more than four. The water drinking test was positive in 26 (14.5 %) of the total glaucoma group, 55 (30.7 %) gave a borderline response. The water drinking test was positive in 9 (3.9 %) of the group with suspected glaucoma, 37 (16.0 %) gave a borderline response.

No statistically significant correlation ($P > 0.05$) was established between the results of the water drinking test and the CPT.

Table IV

Incidence of cataract in 196 eyes of the glaucomatous group and correlation with the cyclopentolate response Responders positive cyclopentolate response rise of IOP ≥ 8 mmHg Borderline rise of IOP 5–7 mmHg Non responders negative cyclopentolate response rise of IOP ≤ 4 mmHg + = incipient ++ = immature +++ = mature or feremature cataract

	No cataract	Cataract of different degrees				Total
		+	++	+++	Total	
Responders	12	6		1	7	19
Borderline	18	12			12	30
Non responders	80	59	5	3	67	147
	110	77	5	4	86	196

The difference between the groups is not significant ($P > 0.05$)

Incidence of cataract in the eyes of the glaucomatous group

Seven responder eyes – every third case – displayed cataract of different degrees To clarify the possible correlation between cataract and a positive cyclopentolate response the incidence of cataract in all the eyes of the glaucoma group was studied (Table IV) No statistically significant correlation ($P > 0.05$) was established between the incidence of cataract and positive cyclopentolate response

Table V

Maximal variation of IOP (Mean ± SD) in the 48 h tension curve in 196 eyes of the glaucomatous group and correlation with the cyclopentolate response

	No of eyes	Maximal variation (Mean ± SD) in 48 h tension curve (mmHg)
*Responders	19	11.74 ± 4.1 mmHg
*Borderline	30	11.36 ± 4.2 mmHg
*Non responders	147	10.44 ± 3.1 mmHg

* Key as in Table IV

The difference between the groups is not significant ($P > 0.05$)

Table VI

Optic disc cupping in 196 eyes of the glaucomatous group and correlation with the cyclopentolate response

Result of the cyclopentolate provocative test	Optic disc					No of eyes
	Normal	Cupping of different degrees				
		+	++	+++	Total	
*Responders	11	7	1	0	8	19
Borderline	16	8	5	1	14	30
Non responders	81	42	21	3	66	147
No of eyes	108	57	27	4	88	196

* Key as in Table IV + = flat cupping of the optic disc to the temporal margin or deep central cupping ++ = temporally marginal deep cupping +++ = total cupping
The difference between the groups is not significant ($P > 0\ 05$)

Table VII

Visual field defects in 196 open angle glaucoma eyes and correlation with the cyclopentolate response

Result of the cyclopentolate provocative test	Visual field					No of eyes
	Normal	Defect of different degrees				
		+	++	+++	Total	
Responders	16	1	1	1	3	19
Borderline	24	0	3	3	6	30
Non responders	101	24	20	2	46	147
No of eyes	141	25	24	6	55	196

Key as in Table IV + = enlarged blind spot incipient Bjerrum s scotoma ++ = opened Bjerrum s scotoma and/or nasal step or even more extensive defect +++ = central or temporal remnant or total loss
The difference between the groups is not significant ($P > 0\ 05$)

Table VIII

Eye findings in 21 eyes with a positive cyclopentolate response Eye findings in the fell... eyes of three patients with unilateral capsular glaucoma and positive cyclopentolate resp... unilaterally are also presented

...o	Age	Sex	Glaucoma diagnosis	Chamber angle	Pigmentation of chamber angle	Pseudo exfoliation	Lens normal 0 catar +	Visual acuity with correction	Opt d...
	44	F	Gl pigmentosum	open	IV	–	0	1 0 (-3 7?)	0
	44	F	Gl pigmentosum	open	IV	–	0	1 0 (-2 5)	0
	62	M	Gl capsul	open	II	++	0	0 4 F	cu...
	44	M	Suspicion of glaucoma	open	III	–	0	1 0 E	0
	73	F	Gl capsul	open	II	+	0	1 0 (+1 0 = cyl)	0
	70	M	Gl capsul	open	II	+++	+++	c f 1–2 m	0
	57	M	Gl simplex	open	I	–	0	1 0 (0 = cyl)	0
	77	F	Gl simplex	open	III	–	+	0 ? (-10 0)	cupp...
	49	F	Suspicion of glaucoma	open	II	–	0	0 8 (-1 75 = cyl)	0
	..1	F	Gl simplex	open	II	–	+	0 4 F	cupp...
	33	M	Gl simplex	open	II	–	0	1 0 F	0
	50	M	Gl capsul	open	III	+++	+	0 15 (1 ?5)	cupp...

Maximal variation of IOP in the 48 hour tension curve in the eyes of the glaucomatous group

The results and correlation with the cyclopentolate response are shown in Table V Maximal variation refers to the difference between the highest and lowest IOP value during 48 hours The variation of IOP was greatest in the responder eyes but there was no statistically significant difference ($P > 0.05$) between the groups

Table VIII

48 h tension curve lowest/medium/ highest/difference (mmHg)	Cyclopentolate test T_0/T_{max}/rise of IOP (mmHg)	Pigment liberat test	Tonography		Water drinking test rise of IOP (mmHg)
			before CPT	during CPT	
I 13/17/22/9	20/40/20	6	0 10	0 10	5
II 14/18/25/11	18/27/9	6	0 10	0 17	6
I 10/15/20/10	20/32/12	6	0 15		7
II 12/17/23/11	15/19/4	6	0 12	0 10	3
21/32/41/20	43/51/8		0 07		4
I 14/17/20/6	14/33/19	6	0 14	0 08	4
II 10/16/20/10	15/29/14	5	0 17	0 04	8
28/31/36/8	30/40/10		0 17	0 24	
30/40/48/18	42/53/11		0 13	0 11	7
20/24/28/8	18/28/10	0	0 20	0 20	3
17/28/36/19	23/37/14		0 05	0 06	10
16/22/26/10	19/28/9	0	0 03	0 09	3
17/29/36/19	25/36/11	1	0 12	0 09	9
15/20 26/11	19 29/10	0	0 23	0 12	6
30/33/43/13	32/45/13	1	0 05	0 04	11

(cont)

Cupping and field loss in eyes of the glaucomatous group

Cupping of the optic disc and the visual field defects were recorded and analysed statistically for all 196 eyes of the glaucoma group Eight of the 21 eyes in the responder group displayed cupping and three eyes glaucomatous field loss of different degrees (Table VIII) No statistically significant difference ($P > 0\ 05$) was demonstrated between the responder group and other groups in cupping of the optic disc (Table VI) or visual field defects (Table VII)

Table VIII (cont.)

Eye findings in 21 eyes with a positive cyclopentolate response. Eye findings in the fellow eyes of three patients with unilateral capsular glaucoma and positive cyclopentolate response unilaterally are also presented

No	Age	Sex	Glaucoma diagnosis	Chamber angle	Pigmentation of chamber angle	Pseudoexfoliation	Lens normal 0 catar. +	Visual acuity with correction	Optic disc
13	64	F	Suspicion of glaucoma	open	II	+ (+)	+	0.25 (+0.5 = cyl.)	pale
14	77	F	Gl. simplex	open	II	–	+	0.3 (+1.0)	cupped
15	55	F	Gl. simplex	open	II	–	0	1.0 (+1.25)	0
16	55	F	Gl. simplex	open	II	–	0	1.0 (+1.5)	0
17	71	M	Suspicion of glaucoma	open	II	+ (+)	0	0.8 (+1.25 cyl.)	0
18	71	M	Gl. capsul.	open	III	++	0	0.8 (+1.75 = cyl.)	cupped
19	68	M	Gl. capsul.	open	IV	++	+	0.7 (–2.0)	cupped
Fellow eye			Normal	open	I	–	0	1.0 F	0
20	61	F	Gl. capsul.	open	III	+	0	1.0 (+3.25)	0
Fellow eye			Borderline	open	I	–	0	1.0 (+3.25)	0
21	66	F	Gl. capsul.	open	III	++	0	1.0 (+1.25 = cyl.)	[illegible]
Fellow eye			Normal	open	I	–	0	1.0 (+1.25 = cyl.)	0

The eye findings in detail and results of the glaucoma investigations in eyes with a positive cyclopentolate response are presented in Table VIII.

Discussion

Responders were encountered in all the age groups – also the younger end (Fig. 1). The mean age of the responder group, 62.3 years, was a few years lower than the mean age of the total series. In the PF group, too, the mean

Table VIII (cont)

Visual field	48 tension curve lowest/medium/highest/difference (mmHg)	Cyclopentolate test T_o/T_{max}/rise of IOP (mmHg)	Pigment liberat test	Tonography before CPT	Tonography during CPT	Water drinking test rise of IOP (mmHg)
hemi anopsia homonym	14/17/26/12	17/26/9	0	0 28	0 10	
defect (+)	20/23/36/16	21/30 9	0	0 11	0 08	11
0	22/27/30/8	22/33/11	0	0 23	0 14	6
0	23/29/34/11	22/30/8	0	0 27	0 16	8
0	14/16/17/3	14/24/10	2	0 17	0 09	3
0	16/20/24/8	20/36/16	6	0 10	0 07	0
defect (++)	27/35/42/15	43/53/10		0 15		11
0	12/17/22/10	18/20/2		0 23		5
0	28/31/33/5	32/47/15	2	0 20	0 20	8
0	21/25/27/6	27/27/0	0	0 23	0.26	3
0	16/23/30/14	21/31/10	6	0 06	0 08	3
0	11/16/22/11	15/ 0/5	0	0 27	0 19	6

age of the responders 68 3 years was a couple of years lower than in the PE group as a whole This was somewhat surprising since we know that degeneration of the pigment epithelium of the iris and pigmentation of the chamber angle increase with age (e g Becker & Shaffer 1965 Duke Elder & Perkins 1966 Leydhecker 1973) similarly PE (Tarkkanen 1962 Aasved 1971 Krause 1973 Krause et al 1973 Forsius et al 1974) On the other hand profuse chamber angle pigmentation (Valle 1976) and PE have been found to be of importance in connection with elevations of IOP as shown in the present work

The responders did not differ significantly from the other patients in age and sex The 93 PE eyes 60 patients represent a typical Finnish material of patients with PE The mean age of the PE patients in Tarkkanen s (1962) large material was 69 4 years The youngest patient was a woman of 46 the oldest one of 89 Two thirds of the patients were female just as in the present material

48 % of the significant IOP elevations during CPT in the total material were encountered in PE eyes with open angle glaucoma (Table I) Marked IOP elevations and concurrent liberation of profuse pigment in the aqueous were reported by Kristensen (1965 1968) during mydriasis test with sympathomimetics on some eyes with capsular glaucoma under treatment Krause et al (1973) also established IOP elevations of ad 17 mmHg in PE eyes during the mydriasis test

A positive CPT response was statistically significantly ($P < 0.01$) more common in PE eyes than in eyes without PE (Table II) There are no reports in the literature on earlier studies of this kind

The material comprised three patients who were found to have unilaterally capsular glaucoma and a positive CPT result (Table VIII) The fellow eyes were negative in two cases for glaucoma and CPT one patient was a borderline case The PE eyes of these patients behaved differently from the eyes without PE as regards both the presence of glaucoma and the cyclopentolate response The observation is interesting since the difference between these eyes was demonstrated in the same persons

In addition to the significance of pigment in PE eyes (Valle 1976) PE material may have a certain role of unknown mechanism in raising IOP

The origin and histochemical nature of PE are not fully known (Blackstad et al 1960 Ashton et al 1965 Horven 1966 Layden & Shaffer 1974) In their histochemical studies Arnesen et al (1963) came to the conclusion that PE material is the result of severe chemicophysiological alterations of the aqueous humour Sampaolesi (1960) found increased fluorescein permeability in the blood aqueous barrier in all PE eyes

It has been shown with fluorescein angiography of the iris (Vannas 1969 1972) and electronmicroscopically (Shakib et al 1965 Ringvold 1969 Vannas 1972) that considerable vascular changes appear in conjunction with the PE syndrome fluorescein leakage from the blood vessels of the iris and vascular proliferation with an abnormal basement membrane which is thin or absent in places and there is abnormal extracellular material around the vessels The vascular endothelium is thin and may display fenestrae (Vannas 1972) It is apparent that changes in the blood aqueous barrier influence the development of abnormal protein in the anterior chamber (Vannas 1972) The viscosity and dynamics of the aqueous and also IOP are possibly altered at the same time

CPT was negative in the majority of the new cases of chronic simple and chronic capsular glaucoma Speaking generally CPT would not seem to be of great importance in the diagnosis of open angle glaucoma since positive re sponses were recorded in only a fairly small proportion (8 / %) of new open angle glaucoma eyes As far as positive responses are concerned the importance of the test is different especially in PE eyes Twenty PE eyes displayed an IOP elevation ≧ 5 mmHg during CPT In 18 of these eyes an immediate diagnosis of open angle glaucoma was established and the remaining two eyes developed capsular glaucoma within two years (Table II) It is an interesting observation that an IOP elevation ≧ 5 mmHg in a PE eye during CPT always signified glaucoma A negative CPT result was not of significance for diagnosis of glaucoma

The water drinking test was positive in 39 (9 0 %) and CPT was positive in 21 (4 9 %) of the 431 eyes in the total material Both tests were positive together in no more than four eyes (0 9 %) (Table III) No statistically signifi cant correlation ($P > 0\,05$) was established between the results of the water drinking test and the CPT The mechanism that causes the elevation of IOP is obviously quite different in these two tests as Kristensen (1968) also reported

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Anaesthesia influences intraocular pressure (IOP) Most of the anaesthetics such as the classical barbiturates lower the IOP In the field of non human primate anaesthesia a new group of anaesthetics became attractive in recent years the cataleptoid anaesthetics *Phencyclidine* is the mother substance of these drugs and is widely used in monkeys *Ketamine* a derivative has also found extensive experimental and clinical use A new cataleptoid agent *CI 744* a combination of a cataleptoid (Tiletamine) and a tranquilizer (Zolazepam) has recently emerged on to the market It has been shown to be an excellent anaesthetic for monkeys and other species (Kaufman & Hahnenberger 1975) For ophthalmological research it is thus of great interest as to whether these drugs affect IOP It was therefore the aim of the present study to evaluate possible IOP effects of three cataleptoid drugs Phencyclidine Ketamine and CI 744 in conscious monkeys A method of conditioning monkeys to allow an applanation tonometry while conscious was described in another paper (Hahnenberger 1976b) Such animals were used here and the IOP measurements in the undrugged state were regarded as the normal values

Material and Methods

Animals Four monkeys (Macaca fascicularis one a female) weighing between 2 2 and 4 2 kg which had been fully trained to allow tonometry while conscious were used These were the same four animals as described in the earlier paper (Hahnenberger 1976b) To test whether it was possible to perform a tonometry without previous training after administration of these drugs about three dozen untrained monkeys of the same species weighing between 1 95 and 3 75 kg were used However the IOP values in the Results section refer only to tonometry performed in trained monkeys

Tonometer The Draeger tonometer (Draeger 1966) used was a slightly modified version previously described (Hahnenberger 1976b)

Tonometry and procedure The method for tonometry used was the standard (continuous method) The plunger is applied to the cornea and the applanation increased continuously until the image indicates an applanation area of 3 06 mm in diameter Since in the conscious animal it is much easier for the right handed author to measure the right eye only this eye was used

Repeated fluorescein administration impaired the visualization of the two half circles so that only about 10 to 15 reliable measurements could be per

formed within a short time i e about 1 h It was thus decided to measure the IOP on only three occasions first just before the drug administration second 15 min after injection and third if possible also 30 min after the injection Each measurement consisted of 2-4 applications and readings which were averaged

All animals received each dose of every drug on at least four occasions and control saline injections at twelve occasions Drugs saline control injections doses and animals were randomized After each experiment at least 48 h were allowed to elapse before the same animal was measured again The drugs were injected intramuscularly in two doses the smallest dose was that which just allowed tonometry in an untrained monkey (tonometry dose = D_T) The second greater dose was deep anaesthetic (surgical) dose (surgical dose = D_S)

Drugs

Phencyclidine (Parke Davis) D_T 0 6–0 7 mg/kg bw D 1.3–1 4 mg/kg bw Phencyclidine was injected as a sterile 2 % solution in 0 05 % chlorocresol

Ketamine (Ketalar® 50 mg/ml commercial solution Parke Davis) D_T 4–6 mg/kg bw D_S 25 mg/kg bw

CI 744 (Parke Davis) D_T 2–3 mg/kg bw D_S 7 5 mg/kg bw CI 744 was injected as 1 % solution in sterile distilled water Oxibuprocaine 0 4 % (Novesine®) was used to anaesthetize the cornea topically
Fluorescein paper strips (Haag Streit) moistened with saline were used

Statistics

The difference between IOP values in the treated and the conscious animal was expressed as percentage of the conscious IOP for each animal and occasion separately and the percentage for the different animals averaged (grand mean)

Results

Control

IOP after saline control injections did not differ substantially from values obtained in the uninjected animal (Table I)

Table I

Influence ıf saline control ınjectı ns l heneyclıdine Ketamine and CI ı44 on the IOP of monkeys Tonometry was performed ımmediately bef re and 1ɔ min and 30 min after drug admınistration P_0 = intraocular pressure of the untreated conscious monkey (mmHg)

Drugs			Mean and range of results at individual occasions								Grand mean and range of averages for individual monkeys	
			Monkey 304		Monkey 322		Monkey 323		Monkey 3?5			
			15	30	15	30	15	30	15	30	15	30
Saline			l₀ = 20 4 (n = 1?)		P₀ = 18 4 (n = 12)		P₀ = ?? 0 (n = 12)		l₀ = 15 3 (n = 1?)			
		mean	-0 2 %	-0 6 %	+1 1 %	-0 3 %	-0 9 %	+2 5 %	-2 8 %	-4 0 %	-0 6 %	-0 4 %
		range	-?9 —	-?4 —	-0 3 —	-1 8 —	-3 4 —	+1 3 —	-4 9 —	-5 7 —	-? 8 —	-4 0 —
			+1 7	+1 3	+2 5	+1 6	+1 6	+3 8	-0 6	-2 2	+1 1	+2 5
l heneycli line	D_T		P₀ = 19 ɔ (n = 4)		l₀ = 18 6 (n = 5)		P₀ = 20 8 (n = 4)		P₀ = 14 8 (n = 5)			
		mean	-0 5 %	-3 8 %	-0 8 %	-3 4 %	-5 1 %	-1 5 %	-4 4 %	-4 7 %	-2 8 %	-3 5 %
		range	-2 5 —	-7 2 —	-2 2 —	-5 0 —	-5 4 —	-3 2 —	-10 6 —	-7 2 —	-5 1 —	-4 7 —
			+1 0	-0 3	+0 6	-1 9	-4 9	+0 2	+1 8	-2 2	-0 8	-3 4
	D_4		P₀ = 18 2 (n = 5)		l₀ = 17 8 (n = 4)		P₀ = ?1 0 (n = 5)		P₀ = 18 8 (n = 4)			
		mean	-1C 4 %	-14 8 %	-18.5 %	-9 0 %	-16 0 %	-1C 6 %	-?? ? %	-16 0 %	-18 7 %	-14 4 %
		range	-19 8 —	-18 ɔ —	?0 8 —	-11.3 —	-?0 —	-?0 0 —	-?7 6 —	-20 2 —	-25 2 —	-16 6
			-13 0	-11 ̣	-1C 1	-C 6	-18 9	-13 4	-?? 8	-11 7	-16 0	-9 0

Ketamine			P_0 = 19 (n = 5)		P_0 = 17.8 (n = 4)		P_0 = 22.6 (n = 4)		P_0 = 15.5 (n = 4)			
	D_T	mean	−14.4 %	−6.8 %	−1.1 %	−2.5 %	−22.0 %	−17.4 %	−32.3 %	−20.0 %	−17.4 %	−11.7 %
		range	−18.9 — −9.9	−9.5 — −4.0	−2.1 — −0.1	−4.3 — −0.7	−23.3 — −20.5	−20.2 — −14.6	−36.1 — −28.3	−26.0 — −14.0	−32.3 — −1.1	−20.6 — −2.5
			P_0 = 19.8 (n = 4)		P_0 = 16.8 (n = 4)		P_0 = 21.8 (n = 5)		P_0 = 14.7 (n = 5)			
	D_4	mean	−27.1 %	−20.3 %	−18.5 %	−9.0 %	−30.5 %	−23.5 %	−37.2 %	−25.8 %	−28.4 %	−20.0 %
		range	−31.4 — −22.8	−21.3 — −19.3	−20.2 — −16.7	−12.4 — −5.5	−33.7 — −27.4	−25.8 — −21.2	−40.5 — −33.9	−29.3 — −22.2	−37.2 — −18.5	−25.8 — −9.0
CI 744			P_0 = 20.4 (n = 5)		P_0 = 17.7 (n = 4)		P_0 = 22.1 (n = 5)		P_0 = 15.3 (n = 5)			
	D_T	mean	−19.0 %	−8.6 %	0 %	+2.7 %	−18.5 %	−7.3 %	−10.0 %	−3.3 %	−12.0 %	−4.1 %
		range	−22.8 — −15.0	−10.5 — −6.8	−1.8 — +1.9	−0.1 — +4.7	−22.3 — −14.8	−11.0 — −3.7	−12.8 — −7.2	−5.0 — −1.7	0 — −19.0	+2.7 — −8.6
			P_0 = 18.3 (n = 4)		P_0 = 16.7 (n = 4)		P_0 = 21.1 (n = 4)		P_0 = 13.9 (n =)			
	D_3	mean	−27.2 %	−22.2 %	−11.6 %	−6.7 %	−28.2 %	−24.2 %	−32.0 %	−26.5 %	−25.3 %	−20.3 %
		range	−29.8 — −24.6	−28.6 — −15.8	−13.6 — −9.7	−8.0 — −5.3	−30.3 — −26.8	−28.9 — −19.5	−35.2 — −28.7	−31.1 — −22.0	−32.0 — −11.6	−20.5 — −6.7

Phencyclidine

With the smaller dose (D_T) of phencyclidine the onset of the effect was slow Within the first 15 min it was not possible to perform tonometry in most untrained monkeys (only two out of the twelve untrained monkeys accepted a tonometry at 15 min) The others showed so very marked defence reactions that they could not be handled properly Twenty five to 30 min after drug administration tonometry became possible provided the animals were treated gently and approached with slow movements Tonometry could thus be performed in 11 out of 12 untrained monkeys This dose induced only a calming effect with obvious visual auditory and pain perception and no anaesthesia. The animals did not adapt a supine position but remained sitting in their cages without evident loss of muscular tone and thus in a perfect condition for tonometry in the way described previously (Hahnenberger 1976b)

In the trained monkeys the IOP was lowered slightly (a few per cent) but the decrease never exceeded 6 % (Table I)

In the surgical dose phencyclidine induced cataleptic anaesthesia without muscle relaxation within 10 min It was thus possible to handle all of 14 untrained monkeys and to perform a tonometry both at 15 and 30 min after drug administration The IOP was lowered by 19 % after 15 min After 30 min the pressure was partly restored the reduction being approximately 15 % (Table I) As the anaesthesia became lighter there was always a burst of nystagmus which occasionally disturbed a proper application of the tonometer But these bursts were only transient and in between them it was possible to measure the IOP in the usual way

Ketamine

In the smaller dose (D_T) Ketamine induced anaesthesia after 10 min Tonometry could be performed in all 14 untrained monkeys tested The animals usually adopted a supine position and seemed to have more relaxed muscles than with phencyclidine In the trained monkey there was a mean IOP fall of about 14 % There was a considerable scatter intra and interindividually After 30 min there was still an IOP reduction (~ 12 % Table I)

The tonometry done as described earlier by holding the monkey between the thighs of an assistant was rather complicated because of the softness of the animal They would accept a headholder with all surgical dosages of the drugs tested and a tonometry could thus easily be performed However to keep the same conditions in respect of the body position of the animal tonometry was always carried out in the erect position

CI 744

With the small dose (D_T) this drug induced a rapid onset of anaesthesia All 12 untrained monkeys tolerated tonometry after 5 min However after 30 min some of them began to recover and showed a strong defense reaction al though none tended to bite In the trained monkeys the effects on IOP were scattered Pressure dropped about ~ 12 % after 15 min (Table I) but had almost recovered at 30 min.

With the surgical dose which provided an excellent anaesthesia all pres sures were decreased on an average between 20 and 25 %.

Discussion

There are only a few studies available dealing with the effect of cataleptoid agents on the IOP Barany (1963) found an average of 17 7 mmHg in the vervet monkey lying on its side treated with 1 0 to 1 2 mg/kg of phencyclidine Krupin et al (1970) with the same drug found an average of about 18 mmHg in Macaca mulatta (dosages were not specified) Since the preanaesthetic values were not available in these studies it is hard to evaluate a possible effect of this drug In the present experiments with the monkey sitting up IOP under phencyclidine was 15 2 mmHg (30 min after injection of 1 2 mg/kg bw phen cyclidine) The species and the tonometer were different but if one allows 1–2 mmHg for the difference in venous pressure due to the position the agreement is surprisingly good It suggests but does not prove that the un anaesthetized IOP s in these species are rather similar

Because of its clinical use Ketamine has been more studied Earlier papers reported no effect on IOP or an increase of IOP in human patients (Corssen & Hoy 1967 Yoshikawa & Murai 1971 Peuler Glass & Arens 1975) In cats there was an increase of IOP after treatment with Ketamine (Hahnenberger 1976a) The present finding in monkeys that IOP is lowered in Ketamine anaesthesia is different The data presented here are too limited for a com plete analysis of the mechanisms underlying differences However there was a marked interindividual scatter This was also seen by Peuler Glass & Arens (1975) Although they reported no IOP effect on an average there was a marked interindividual scatter ranging between +41 % and −35 %, 10 min after injection of the drug Since CI 744 is a mixture of a cataleptoid ana esthetic and a diazepinone the pressure lowering effect can only be partially ascribed to the one or the other of the components (Hahnenberger 1976a)

The fact that with all drugs tested the IOP was lowered suggest the possibility of a systematic error. It has to be considered that the animals were possibly never completely trained and that there was always some degree of anxiety which could have raised the real IOP giving a false normal IOP. With anaesthesia the anxiety component would be eliminated and a false drop in IOP would be apparent. This would be an unspecific anaesthetic effect. However, the animals always displayed very stable IOP values in the conscious state and even after a break of several weeks between measurements they had essentially the same pressures. Also the effect of saline treatment was negligible.

The present paper has shown that cataleptoid agents lower the IOP. In the lower dosage phencyclidine was virtually without effect. From the standpoint of tonometry phencyclidine thus seems to be the drug of choice because it also provides a kind of anaesthesia which is very suitable for tonometry if the method as described earlier is to be used.

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EPISCLERAL VENOUS PRESSURE AND FLOW DYNAMICS

BY

JOHANNES WIDAKOWICH

Episcleral venous pressure was measured by means of an air jet at different levels of occlusion of the measured vessel
This was repeated at different points in one branching venous plexus system
The results indicate that the most reliable estimate of the pressure is obtained at the pressure level at which the blood column becomes somewhat paler
Occlusion of the vessel causes a rise in venous pressure which may be considerable especially in large veins

Key words episcleral venous pressure – air jet – episcleral venous dynamics (aqueous dynamics)

In a previous paper a method for measuring the pressure in episcleral vessels by means of an air jet was described by Krakau et al (1973) The force needed to compress the vessel to a given degree is obtained by means of an air jet. By increasing the air flow the external pressure on the vessel is increased The effect of the air stream on the vessel was graded thus

0 – no effect
\+ = slight deformation of the vessel
++ – clear effect with reduction of the blood stream to about half its width
+++ = total obstruction of the vessel with the blood stream seemingly cut off

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However even *at this* level blood corpuscles pass the collapsed area and total stagnation is reached first at a still higher pressure

Krakau et al (1973) concluded that at the + level a pressure lower than that in the vessel is recorded and that the +++ level is higher than the actual pres sure in the vessel while the ++ level would give the best estimate of the pres sure in the vessel This level however is not very well defined

The following studies were conducted in an attempt further to evaluate the method and to analyze the pressure dynamics in the vessels concerned

Method

In these studies on the sequence of events seen on the aqueous vein (Ascher 1942) while increasing the pressure on it by means of an air jet it was found that the earliest detectable change is that the blood column becomes somewhat paler This will be called level a in the following and it is analogous to the + level

Table I
Serial measurements at the same point of a vessel

Reading No	Level			
	a	b	c	d
1	*1 21*	*1 86*	*2 21*	*2 70*
2	1 25	1 64	2 17	_ 58
3	*1 17*	*1 70*	*1 94*	2 47
4	1.33	1 86	2 17	2 47
5	1.25	2 17	1 94	2 70
6	1 17	1 70	2 17	
7	1 09	1 78	1 86	
8	*1 17*	*1 86*	*1 94*	
9	*1 17*	*1 70*	2 09	
10	1 17	1 78		
MP	1.20	1 81	2 05	2.58
SD	0 083	0 159	0 139	0 120

MP = mean pressure. SD = standard deviation

Points of measurement for levels a and b are identical and different from those for levels c and d which are identical Subject KS

Values in kPa transformed from a reading in cm H O on the water manometer
1 kPa = 7.50 mmHg

Table II

Serial measurement of a and d levels at the same point of a vessel

Reading No	Level a	Level b
1	0.92	1.75
2	0.92	1.54
3	0.75	1.50
4	0.79	1.42
5	0.83	1.63
6	0.67	1.58
7	0.71	1.54
8	0.92	1.46
9	0.83	1.25
10	0.79	1.33
MP	0.81	1.50
SD	0.096	0.158

MP = mean pressure SD = standard deviation

Points of measurement for levels a and d are identical. Subject TI

Values in kPa transformed from a reading in cm H_2O on the water manometer

1 kPa = 7.50 mmHg

When the colour saturation is estimated to be 50% level b has been reached.

When the width of the vessel decreases to 50% level c has been reached.

Finally there is total obstruction to flow with no passage of blood corpuscles through the measured segment. This is called level d or the stagnation level. To reach this last point takes some time and the pressure is rather high, with the result that when repeated measurements are made it gives discomfort to the eye in the form of a burning sensation. Furthermore the conjunctival tissue becomes somewhat hazy and opalescent, making inspection of the vessel more difficult. This may be due to the drying out of the tissue by the air stream.

The a, b and c levels are estimated rather subjectively; the change from no effect on the vessel through levels a, b and c occurs gradually and the points are difficult to define exactly, whereas the d level is clearly defined – the blood flow through the segment on which the measurement is made has either ceased or it has not.

Measurement were made in red free light.

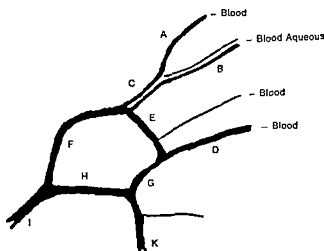


Fig 1

Drawing of the anastomosing episcleral veins used for measuring Letters are for identification of measurement points Direction of flow from A B and D towards I and K

Table III

Measurement of the a and d levels at different points of a ramifying conjunctival vein

	Level	
	a	b
Point A	0.75	1.46
B	0.75	1.46
C	0.75	1.46
D	0.75	1.62
E	0.75	1.42
F	0.75	1.92
G	0.71	1.88
H	1.00	2.25
I	0.75	2.67

Subject TL

Values in kPa transformed from a reading in cm H_2O on the water manometer

Every value is a mean of three to five measurements

1 kPa = 7.50 mmHg

33

Table IV

a and d levels for episcleral venous pressure in six different nonglaucomatous eyes

Eye	Vein	Level a	level d	IOP
1		1 25	2 86	3.33
2		1 64	3 31	2 13
3		1 17	3 76	2 66
4	I	0 84	1 76	
4	II	0 84	1 84	
4	III	0 92	1 84	
5	I	1 09	2 80	
5	II	1 25	2 31	2 00
6	I	1.30	2 16	
6	II	0 88	1 61	

Measurements were made as close to Schlemm s canal as possible
In eyes Nos 1 2 and 3 only one vein was measured In eye No 4 veins I and II lie close to each other nasally situated Vein III is temporally situated In eye No 5 two different veins were measured In eye No 6 vein I lies temporally and vein II nasally Every value is a mean oof three to five measurements
Values in kPa for episcleral venous pressure transformed from a reading in cm H_2O on the water manometer for IOP transformed from a reading on the Goldmann applanation tonometer
1 kPa = 7 50 mmHg

Material

The eyes of two healthy individuals KS female 25 years old and JT male 38 years old were used for the measurements described in Tables I II III and Fig 1

Six nonglaucomatous eyes were used for the measurements described in Table IV

Results

The a b c and d levels were determined in a series of consecutive measurements at the same point on the vessel The results are seen in Tables I and II

In Table I the series for level d is short since the d level measurements were discontinued because of discomfort in the subject s eye

In Table II the last two values for the d level are uncertain because of beginning cloudiness of the conjunctival tissue overlying the vessel

The a and d levels were determined at different points on a ramifying conjunctival vein Fig 1 shows the measuring points and Table III shows the values recorded

At each point the readings were first made at the a level then at the same places at the d level whereafter at some points the a level was checked and was found to be unaltered in spite of hyperaemia in the region

Three to five measurements were made in sequence at each point and the mean values were used

The a and d levels were determined for 10 different aqueous veins in six different eyes (Table IV) The points of measurement were chosen as close to Schlemm's canal as possible

Discussion

The results in Table I show that levels a and d seem to be easier to define precisely than levels b and c

However it should be borne in mind that level a values as was pointed out by Krakau et al (1973) are expected to be lower than the true values for the episcleral venous pressure The results in Table III indicate that a level values in the small and large episcleral veins are similar while d level readings vary greatly from one vein to another and are higher in the larger veins than in the smalled tributaries The true pressure of course is slightly lower in the larger veins

This suggests that the error introduced by measuring the stagnation values tends to increase with the size of the vein This could be explained thus When a vessel is obstructed a quantity of blood is forced into collateral pathways These seem to have a capacity sufficiently great to accommodate the increased blood flow with a minor pressure rise when dealing with small vessels In the larger vessels on the other hand it seems as if the collateral capacity is smaller and a rise in pressure results when the flow paths are altered by obstructing the vessels at the measuring point

If the a and d levels differ little in value at a point there are sufficient anastomotic vessels to accommodate the blood without a pressure rise while the opposite situation pertains when the a and d levels differ more

Brubaker (1967) compared direct cannulation with a torsion balance method and a pressure chamber method both modified from former types (Goldmann 1951 Linnér 1949) Brubaker used two fundamentally different types of cannulation Distal cannulation denoted introduction of the cannula into the lumen away from the limbus and in the direction of flow

Proximal cannulation denoted introduction of the cannula into the lumen toward the limbus and against the direction of flow

Brubaker stated that preliminary studies of direct cannulation showed that the results from proximally placed cannulas were in some cases influenced by the level of the intraocular pressure

Distal placement was therefore chosen for all subsequent studies and these showed good agreement between the values for direct cannulation and the pressure chamber method For theoretical reasons it can be assumed that the values for proximal cannulation are more related to stagnation or d level values while values for distal cannulation are more related to a b and c level values

Thus stagnation level values obtained with the air jet method cannot be compared either to Brubaker s values for distal cannulation or to values obtained by the pressure chamber method

The results in Table IV indicate that even in small veins a and d levels differ from eye to eye and as in the case in eye No 6 the pressure may be different in different venous systems in the same eye both at the a and at the d levels It should be noted that a and d levels represent measurements of pressures during two distinctly different conditions The values can never be compared to each other in the sense that they have a given relation to one another

The results of the present study indicate that in measuring the episcleral venous pressure by means of an air jet it is advisable to measure both a and d levels in a vein as close to Schlemm s canal as possible

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READAPTATION TIME AFTER PHOTO STRESS

Readaptation Time as a Function of Oxygen Concentration

BY

B TENGROTH B HÖGMAN C J LINDE and H BERGMAN

Optokinetic nystagmus (OKN) is used to study the eyes ReAdaptation Time (RAT) after a brief exposure to a light flash
The effects on RAT of breathing different concentrations of O are examined
Significant changes in RAT have been registered showing that inhalation of 100% O as compared with room air results in a shortened RAT (i e improvement) while inhalation of 9% O leads to an increased RAT (i e impairment)
The physiology of RAT and the possible mechanisms behind the changes caused by different O concentrations are discussed The findings of this group are compared with those of other studies

Key words ocular readaptation time – glare recovery – optokinetic nystagmus – oxygen concentrations

Previous Studies

The visual system like the nervous system as a whole is very sensitive to hypoxia and to toxic agents Binocularity as well as visual perception are often affected by detrimental agents in the environment

Earlier O studies have for the most part dealt with hypoxia (Gellhorn 1936

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Evans 1938 McFarland & Halperin 1939 Reybour 1941) These investigators have all concluded that hypoxia causes a decline in visual acuity accompanied by dimming of the visual field They have further linked hypoxia with impairment of absolute thresholds as well as the dark adaptation threshold and a reduction of intensity discrimination Other studies have been conducted on the effects of the inhalation of high O concentrations on visual performance McFarland & Halperin (1939) noted a slight improvement of foveal visual acuity in subjects who had inhaled 100 % O However Gallagher (1965) was unable to register any changes in visual acuity flicker fusion dark adaptation visual fields or ERG following inspiration of high O concentrations Connors (1968) could not show any improvement of foeval detection thresholds in subjects who inhaled 100 % O for periods of up to one hour Direct measurements have also been made of vascular changes induced by different concentrations of O Cusick Benson & Boothby (1940) found a 20 % reduction of the caliber of retinal arterioles in subjects inhaling 100 % O Despite this change in caliber the retinal tissues in fact received an increased supply of O under these experimental conditions When subjected to hypoxia the retinal vessels dilated The changes in cerebral blood flow due to different arterial O tensions have been shown to be autoregulated an organ being able to maintain its own blood supply despite changes in blood O content (Haggendal et al 1969) This autoregulation however often disappears at very low and very high oxygen tensions

The mechanism of autoregulation is believed to be mainly myogenic in nature and metabolic factors play a major role Alm & Bill (1972) have obtained results indicating that retinal blood flow like its cerebral counterpart is also efficiently autoregulated Their investigations have also shown that O induces vasoconstriction in retinal vessels and that low CO tension causes vasoconstriction while high CO tension leads to vasodilatation

But retinal autoregulation just like the cerebral one does have its limitations There is an arterial O pressure limit of about 40–50 mmHg below which retinal blood flow actually is decreased And most likely there is a similar limit for autoregulated vasoconstriction allowing an increase in flow at very high PaO values There are reports of increased O saturation in retinal venous blood in humans inhaling 100 % O (Hickam et al 1959)

Evans et al (1968) investigating the effects of high concentrations of O on dark adaptation and glare recovery time noted a significant shortening (i e improvement) of these values Visual field size was not affected Observations made in our laboratory showed that inhalation of 15 % O increases glare recovery time while inspiration of 100 % O decreases (i e improves) that time (Hogman et al 1974)

In an attempt to study cerebral degradation investigators have used methods such as flicker fusion glare recovery time and fusion lock (Severin et al 1963 Blomberg et al 1966 Evans et al 1968)

Most of these studies have shown considerable variation in the results obtained making these methods less than useful Severin et al (1963 1966) found that registration of glare recovery time (also known as the photo stress test) can supply a statistically reliable estimate of macular function In certain diseases involving an impaired retinal circulation or the destruction of photo receptors there was a prolongation of glare recovery time (Severin et al 1967)

Glare recovery time or readaptation time (RAT) appearing to be the most sensitive of the methods mentioned this group decided to develop an improved RAT assessment technique for studying visual perception in man Glare can be defined in a number of ways and mean different things In the context of this paper glare can be considered synonymous with photo stress

The aim of this paper is to present an objective method for registering RAT Using this method a study was made of the effects on RAT of the inhalation via open mask of different O concentrations

Determination of RAT

The eye s readaptation time (RAT) is a function of the central nervous system probably both on a retinal and a cerebral level RAT can be registered in a variety of ways In the most common method the subject presses a button when perceiving the target after exposure to glare Another technique in which the active cooperation of the subject is not needed involves the use of an optokinetic stimulus e g a rotating drum painted with alternating black and white vertical bands When subjected to this stimulus the eyes will move in a characteristic pattern called optokinetic nystagmus (OKN) A slow pursuit movement is followed by a rapid refixation The OKN can easily be registered by using an electrooculograph (EOG) The frequency of OKN increases as the velocity of the optokinetic stimulus increases but only up to a certain point after which the OKN frequency remains constant over a wide range of stimulus velocity Further velocity increases result in fusion of the optokinetic pattern and a termination of the OKN

When a subject is exposed to glare perception of the optokinetic stimulus is no longer possible and the OKN disappears After a certain period of time (RAT) the OKN reappears with the same frequency and amplitude

A significant advantage of the method using OKN to register RAT is that

this technique eliminates the considerable variations in RAT caused by the subject's inability to stick to consistent criteria when announcing perception of the target It further does away with the reaction time involved when the subject presses a button

Method

The apparatus for registering RAT via OKN (Fig 1) functions in the following manner The subject is dark adapted to the luminance of the optokinetic stimulus (3×10^{-4} cd/m scotopic level) The direction and velocity of the stimulus can be varied A light flash (diameter 55°) produces a glare which hits the subject's eyes while these are directed straight ahead The luminance of the flash is 2×10^{4} cd/m² and its duration 0 8 ms

Once the OKN has been induced the eye movements automatically trigger the glare flash to occur in the middle of the slow phase of the OKN This is crucial because the retina has to be exposed in the same fashion each and

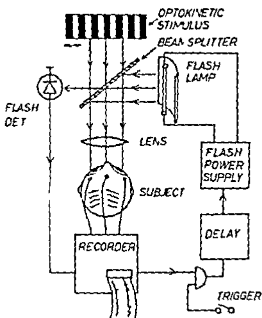


Fig 1
Set up used for registering RAT

every time with the glare image covering a larger retinal area than the opto kinetic target image When the periphery of the retina is not stimulated by the glare image the stimulus target will be picked up and OKN induced The optokinetic target changes direction at the time of the glare flash to avoid con fusion with a possible darknystagmus The OKN is recorded via EOG elec trodes and registered on a Siemens mingograph The light flash is indicated on a separate channel The entire apparatus has been described in detail previously by Hogman et al (1972)

The RAT is easily calculated by measuring the elapsed time from the glare flash to the reappearance of the OKN (Fig 2) The reliability of a single RAT measurement has been estimated from results of a sample of 56 persons The group included 40 males and 16 females ranging in age from 17 to 59 The reliability estimate was based on a repeated measurement analysis of variance done on three consecutive RAT values recorded at five minute intervals No adjustment was made for different mean values of RAT Using the formula below (Winer 1971) a reliability coefficient of 0 87 was calculated indicating adequate measurement precision

$$\text{Reliability of a single measurement} = \frac{MS_{\text{between subjects}} - MS_{\text{within subjects}}}{MS_{\text{between subjects}} + (K-1)MS_{\text{within subjects}}}$$

The test group was composed of six male subjects (25–31 years old) who inhaled the air through an open mask Four different O concentrations were used (9 % 15 % 20 % and 100 %) The two lower concentrations were mixed with helium

A catheter was inserted into the left radial artery of each of three subjects and blood samples were taken before exposure to the different O concentra

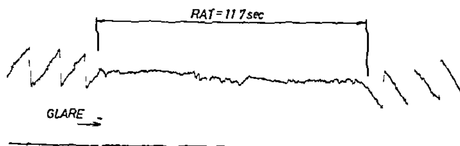


Fig 2
OKN registered by EOG technique

tions Arterial capillary blood was taken from the fingers of the remaining three subjects Each subject was then in turn placed in a dark room where the experiment was first conducted while 9 % O_ was being administered for a period of 20 min The RAT was registered after 10 15 and 20 min and blood samples were taken simultaneously The same procedure was then repeated with each of the other three O concentrations PaO_ was determined with a polarographic electrode and PaCO with a glass electrode (BHS 3 Mk 2 Radiometer Copenhagen)

Results

The mean RAT values are shown in Table I

The values at different O concentrations represent the means of the three results obtained at the time intervals of 10 15 and 20 min The blood sample analyses for PaO PaCO and pH shown in Table I are the means of three measurements

Fig 3 illustrates the RAT changes at different O_2 concentrations as a function of PaO The curve shows a regression line with the upper and lower confidence levels (95 %) calculated by the least square method The regression line is based on the mean values of RAT and PaO at each of the four different O concentrations The product moment correlation coefficient between RAT and PaO is 0 94 and the confidence levels are at ± 1 01 seconds

When inhaling O in concentrations lower than that in room air (21 7 % O) the subjects showed an increase in the RAT as compared to room air The RAT

Table I

Means of RAT PaO PaCO and pH (N = 6)

O concentration in the air	9 %	15 %	20 %	100 %	Room air (21 7 %)
RAT (seconds)	11 81	9 56	8 84	7 09	8 47
PaO (mmHg)	48 5	64 3	80 4	3 9.5	8[illegible]7
PaCO (mmHg)	[illegible]9 1	3_ 5	3[illegible]5	30 8	34 0
pH	[illegible] 46	7 48	7 42	7 43	7 43

The individual mean values are based on 3 measurements

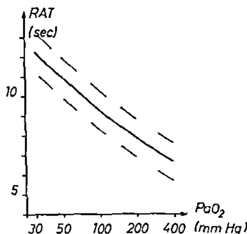


Fig 3
RAT as a function of PaO_ Confidence limits at 95 %

increased from 9 6 seconds at 80 mmHg PaO_ (20 % O) to 10 9 seconds at 47 mmHg (9 % O) Inspiration of 100 % O (330 mmHg PaO) leads to a decrease in RAT for all subjects RAT decreased from 9 6 seconds at 20 % O to 6 9 seconds at 100 %

The PaO varies as a function of the oxygen content of the inhaled air while the pH values were not noticeably affected by the changes in O concentration

The pH was calculated to be 7 43 on the average

The somewhat low PaCO values recorded during inhalation of the different gas mixtures are probably explained as a stress hyperventilation due to the face mask which was not used when room air was inhaled

Discussion

Brief intense light flashes causing photo stress or glare probably result in a number of physiological events in the receptor cells of the retina as well as in the visual pathways and cerebral centers The details of these supposed phenomena are not known Preliminary experiments indicate that the eye s photochemical processes play a minor role in the RAT The crucial preadaptation time 30 min used in most studies of adaptation to normal light levels does not seem to be of significance in our study since it can be varied between 5 and 30 min without affecting the RAT

Further evidence indicating that an adaptation mechanism other than the

photochemical one lies behind the results of the glare recovery tests can be found in the observation that ordinary night vision tests show results which display no correlation to the RAT (Marmolin 1976) The relationship between the RAT and the PaO_2 is shown in a curve with a fairly small variance It is not clear whether this relationship reflects photochemical or neurophysiological phenomena However earlier studies (McFarland 1939 McDonald 1939) suggest that changes in PaO_2 do not affect the regeneration of photopigments but more likely influence processes in the neuronal pathways and in cortical centers According to McFarland s experiments the return to normal (after O_2 depriva tion) of the PaO_2 results in a sudden recovery of visual sensitivity in the dark adapted eye. That this recovery takes place in the absence of any changes in the dark environment indicates that no regression of visual pigments could have taken place McFarland also noted that the elevation in adaptation thres hold induced by a low O_2 concentration is largely reversed within some two min after the inhalation of very high O_2 concentrations It is unlikely that a photochemical regeneration can occur so rapidly

The changes in the dark adaptation curve caused by hypoxia and those induced by vitamin A deficiency were found by McDonald (1939) to be dis similar Accordingly he suggested that two different processes were involved in the visual response This conjecture was substantiated by the observation that vitamin A deficiency did not alter the effect of low O_2 on the adaptation threshold McDonald concluded that since hypoxia did not affect the photo chemical process in which vitamin A is involved it must act elsewhere in the visual system

The effects on the RAT of changes in PaO_2 can be explained in a number of different ways Acute hypoxia may result in false responses because of changes in the subject s state of consc ousness However in our experiments the subjects did not exhibit any symptoms which could be attributed to such a change in consciousness

Another explanation for the effects on the RAT of changes in PaO_2 can be sought in the well known observation that cerebral centers are extremely sensitive to changes in PaO_2 It is therefore not surprising that the retinal tissue being part of the cerebrum is also very sensitive to such changes (Weinstein 1937)

Two different types of mechanisms can be conceived to explain the effects on the visual system of different concentrations of O_2 One possible mechanism could involve direct action on nervous tissue another could operate via changes in the circulatory system It has been reported that the compensatory auto regulation of the cerebral circulation (Haggendal et al 1969) and that of retinal tissue (Alm & Bill 1972) can prove to be inadequate especially in the presence of a significant decrease or increase in PaO_2 In our experiments

PaO_2 values ranged from 49 mmHg to 330 mmHg with PaO_2 at these two extremes probably impairing circulatory autoregulation

It is an established fact that oxygenation of a hypoxic subject will result in an improved visual sensitivity (McFarland & Halperin 1940 McFarland & Forbes 1940) However it has not yet been demonstrated that high O_2 concentrations will lead to an improvement of normal visual functions In most previous studies purely retinal functions had been investigated (McDonald 1939 McFarland & Halperin 1940 McFarland & Forbes 1940 Gellhorn 1942) The phenomena involved in our study however may well embrace cerebral function in general

As stated earlier changes in PaO_2 affect cerebral perception centers either directly or through changes in the circulatory system The fact that the OKN is used as an end point and that this reflex may be cortical or subcortical in origin does not in any way influence our results since the OKN remains completely unaffected by the different experimental conditions However the time element involved in the perception of the optokinetic stimulus and the time lag until the OKN begins can of course be influenced by changes in PaO_2 One hypothesis suggests that hypoxia as well as an increased oxygenation of the blood can affect both the retinal and the cerebral processes involved in RAT A similar effect on the photochemical processes is less likely but cannot be excluded

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THE OCCURRENCE OF MACROPHAGES IN THE ISCHAEMIC RABBIT EYE

BY

NEIL F JOHNSON

Mature macrophages involved in the removal of outer segment material were found between the visual cells and retinal pigment epithelium of the ischaemic rabbit retina The mature macrophages were evident after only 15 min of ischaemia and the cells became progressively more numerous with increasing periods of ischaemia A quantitative study was undertaken into the occurrence of the macrophages These cells were probably of retinal pigment epithelial origin

Key words ischaemia – macrophages – outer segment material – retinal pigment epithelium

Ischaemia is often accompanied by degenerative changes in the visual cells especially in the outer segments This degeneration can result in considerable outer segment debris being present in the sub retinal space particularly after prolonged ischaemic episodes The presence of this debris is frequently associated with mature macrophages in the sub retinal space (Johnson 1974 1976) This paper describes the removal of outer segment debris by the macrophages

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Material and Methods

The material and methods employed in this study were identical to those described in two previous papers (Johnson 1975 Johnson & Grierson 1976) Material was obtained from eyes made ischaemic by raising the intraocular pressure sufficiently to abolish the blood flow to the eye (Johnson 1975) or by complete section of all the vessels supplying the eye The latter material was obtained from a study of post mortem changes in the retina in which the tissue was maintained for varying periods at either room temperature or at 37 C (Johnson & Grierson 1976) The number of eyes investigated is indicated in Table I

Material for electron microscopy was cut with a L K B III Ultramicrotome and 400–600 Å thick sections were stained with uranyl acetate and lead citrate The specimens were investigated with a Siemens I A Elmiskop I micron thick sections were stained with Loeflers methylene blue followed by alcoholic differentiation for light microscopy

Results

Light micro copy

Macrophages were apparent in all the ischamic tissue irrespective of the method used to induce ischaemia (Figs 1 a 1 b and 2) The cells were 10–25 microns in diameter with an ovoid nucleus 5–12 microns in diameter (Fig 1 b) The nucleus often possessed a prominent chromatin mass The cytoplasm of the macrophages was vacuolated and contained many small (up to 3μ in diameter) dark staining inclusion bodies All the macrophages appeared to be

Table I
Table showing the number of eyes investigated

Period of ischaemia (min)	Pressure induced ischaemia	Post mortem (37°C)	Post mortem (room temperature)
15	3	3	3
30	3	2	3
60	2	2	2
90	2	2	3
120	2	2	2

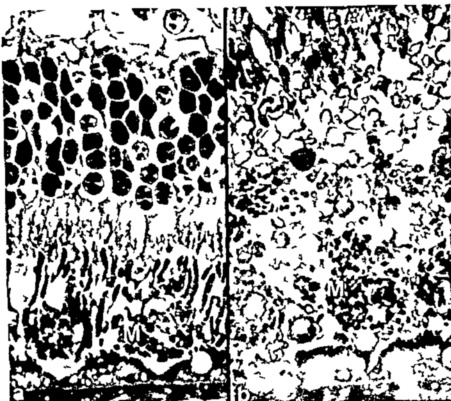


Fig 1

Light micrograph showing macrophages in the sub retinal space of ischaemic retina
a) 60 min pressure induced ischaemia showing solitary macrophages (M) amongst disorganised visual cell outer segments (OS) × 1500
b) 120 min pressure induced ischaemia showing clumped macrophages (M) amongst severely disrupted and fragmented outer segments (OS) × 1500

mature and were adjacent to the apical surface of the retinal pigment epithelium The number of macrophages increased with increasing periods of ischaemia Following the longer periods of ischaemia the macrophages were frequently found in clumps (Fig 1 b) whereas with the shorter periods the cells were solitary (Fig 1 a) The longer periods of ischaemia were associated with pronounced discruption of the visual cells outer segments The nature of the increase in number of macrophages has been determined by counting the number of these cells occurring in 100 mm of tissue obtained from the peripheral retina Sections were cut at 25 μ intervals to avoid the possibility of counting the same cell twice The results are shown in Fig 6 In all three

cases the number of cells increased with increasing the period of ischaemia Following 15 min ischaemia the macrophages were rare while after 120 min ischaemia theye were commonly found In the three groups of tissue the increases were of the same order although the cells were more frequent following periods of pressure induced ischaemia than in the post mortem tissue In the latter tissue macrophages were more frequent in the tissue maintained at 37 C

Electronmicroscopy

Electronmicroscopy confirmed the light microscopic findings A prominent feature of the cytoplasm was the many inclusion bodies (Fig 3) They consisted almost entirely of phagosomes containing outer segment material (Fig 4 a)



Fig 2

Light micrograph of post mortem tissue maintained at room temperature for 60 min showing mature macrophages (M) in the sub retinal space × 1,500

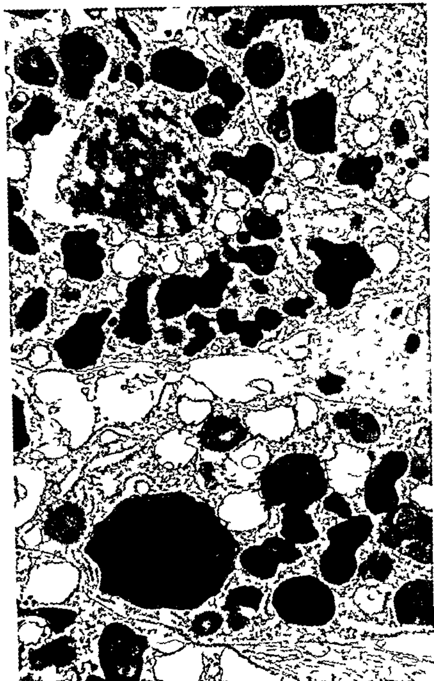
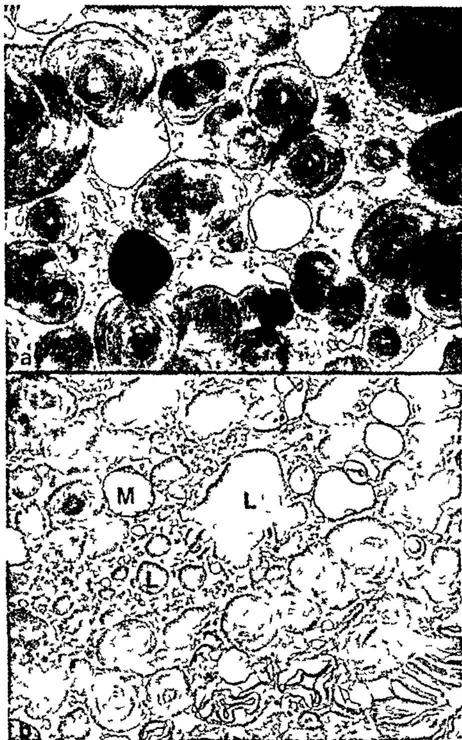


Fig 3

Electron micrograph of macrophages following 190 min pressure induced ischaemia
× 8000


a
M
L
L
b

The inclusion bodies were similar to some phagosomes present in the retinal pigment epithelium A similarity existed between the pigment epithelial phagosomes involved in the early stages of degradation of outer segment material as described by Bairati & Orzalesi (1963) and Špitznas & Hogan (1970) An unusual feature of the macrophagic phagosomes was the presence of more than one fragment of outer segment material (Fig 4 a) In the retinal pigment epithelial phagosomes only one such fragment was encountered

The macrophagic cytoplasm contained many distended mitochondria with an electron translucent matrix and disrupted and shortened cristae (Fig 4 b) In some instances the mitochondrial membranes were ruptured Many membrane bound vesicles occurred within the cytoplasm (Fig 5 a) Amongst the various types of vesicles were found smooth and coated vesicles and lysosomal like bodies The smooth vesicles varied considerably in size (0 02–0 15 microns in diameter) and were more numerous around the Golgi apparatus which was often well developed (Fig 5 a) The coated vesicles were found more generally distributed throughout the cytoplasm The lysosomal like bodies contained a granular electron dense substance and were irregular in shape and variable in size (0 2–2 0 microns) (Fig 4 b) The membrane systems were not particularly well developed The rough endoplasmic reticulum was more prominent than the smooth endoplasmic reticulum The cell membranes were often thrown into finger like projections which were frequently compressed between adjacent cells (Fig 5 b) The cells lacked a basement membrane and had a smooth outline free of pinocytic vacuoles

The ultrastructural features suggest that these cells were mature macrophages involved in the removal of outer segment material

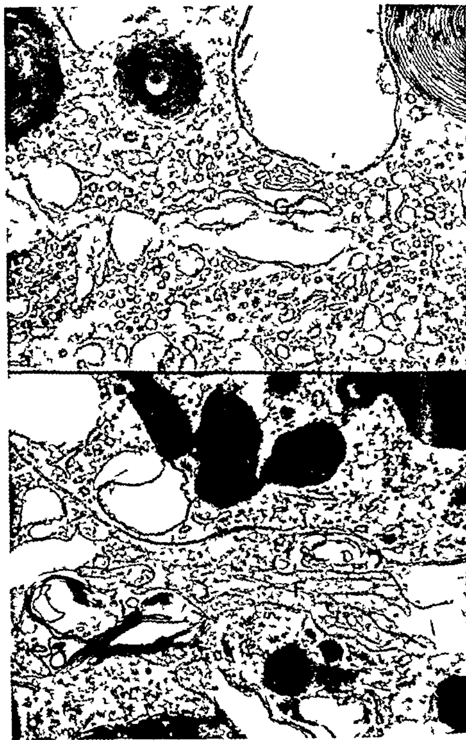
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Fig 4

Electron micrographs of the cytoplasmic contents of the macrophages

a) Many phagosomes occur which contain outer segment material often more than one fragment of material is enclosed within the phagosome (90 min pressure induced ischaemia × 30 000

b) Lysosomal like bodies (L) are numerous within the cytoplasm and are irregular in shape and size Distended mitochondria (M) also occur in the cytoplasm (60 min pressure induced ischaemia) × 15 000



Discussion

A prominent feature of complete retinal ischaemia is the presence of mature macrophages in the sub retinal space Even though the retina is no longer nourished by fresh blood some cells of the retina or choroid are able to proliferate and engulf outer segment material Speculation exists concerning the site of origin of macrophages in the outer retina Free and fixed macro phages are generally thought to arise from circulatory monocytes although they can derive from tissue histocytes and in the central nervous system from microglia (Carr 1974) A circulatory origin for the retinal macrophages in this instance may be unlikely In both the pressure induced ischaemic and post mortem tissue the blood flow to the eye is abolished The macrophages would have to transform from the small number of monocytes occurring in the blood trapped within the eye There was no evidence of any transforma tion of monocytes into macrophages which one would except if the latter cells were of circulatory origin In addition the number of circulating white blood cells may have been reduced in the pressure induced ischaemic tissue by the use of urethane as the anaesthetic agent (Haddow & Lexton 1946) A histiocytic or microglial origin of the macrophages would also seem unlikely in view of the small number of such cells found in the choroid and retina respectively as well as the lack of evidence of their migration and trans formation The retinal pigment epithelium appears to be a likely source of the macrophages Although the exact way in which they could be derived from the pigment epithelium is unknown Whatever the mechanism for the formation of these macrophages it must occur rapidly as the cells are seen after only 15 min of ischaemia The rapid appearance of these mature macrophages may preclude transformation from a cell type not already involved in phagocytosis The retinal pigment epithelium is able under normal circumstances to engulf outer segment material If the site of origin is the retinal pigment epithelium (RPE) then the retinal macrophages may be whole RPE cells which have migrated from their attachment to Bruch s membrane a cell budded off from the RPE or cells formed by very rapid mitosis In spite of the considerable amount of tissue investigated no evidence was seen for any of the above mechanisms

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Fig 5

Electron micrographs of the cytoplasmic contents of the macrophages

a) Many small smooth vesicles (S) occur especially adjacent to the Golgi apparatus (G) (120 min pressure induced ischaemia) × 30 000

b) The cell wall is often thrown into finger like projections (F) which are often com pressed between adjacent cells (120 min post morten room temperature) × 35 000

Marshall Laukhauser Lotmar & Roulier (1971) speculate that proliferation of the RPE at the edge of a photocoagulation lesion occurred by cell budding as they found no evidence of rapid mitosis or incorporation of ^{3}H thymidine during epithelial regeneration However Gloor (1969) Wallow & Tso (1973) Ishikawa Uga & Ikui (1973) and Ishikawa & Ikui (1974) have shown mitotic figures in proliferating RPE cells

Macrophages in the sub retinal space also occur following photic damage (Tso 1973) light coagulation (Gloor 1969) damage resulting from radiant energy (Friedman & Kuwabara 1968) and cryosurgery (Lincoff & Kreissig 1971) Their origin has been considered to be the monocytes circulating in the choriocapillaries (Tso 1973) the retinal histiocyte (Friedman & Kuwabara 1968) and the retinal pigment epithelium (Gloor 1969 Lincoff & Kreissig 1971)

An interesting aspect of this study was the appearance of macrophages even after prolonged periods of ischaemia The number of macrophages increased with increasing durations of ischaemia This increase in number paralleled the degree of damage observed in the outer segments The difference in the number of cells occurring in the pressure induced ischaemic tissue and that in the post mortem tissue maintained at room temperature was not understood The degenerative changes in the outer retina appeared similar in post mortem tissue maintained at room temperature compared

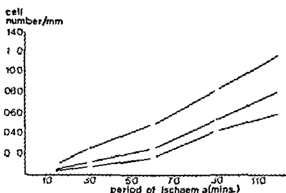


Fig 6

Graph showing the number of macrophages occurring in 100 mm of retinal tissue from the peripheral retina following varying periods of ischaemia

■ Pressure induced ischaemic tissue

● Post mortem (room temperature) tissue and

▲ Post mortem (37 C) tissue

to that kept at 37°C may be a reflection of the presumed greater metabolic activity in the latter

This study has shown that mature macrophages are a feature of complete retinal ischaemia and that these cells are more frequently seen following prolonged periods of ischaemia The cells are of probable epithelial origin and are concerned in the removal of outer segment debris The macrophages readily disappear on restoration of the blood supply (Johnson 1976) and the retinal pigment epithelium is then concerned with removal of the outer segment debris (Johnson 1975)

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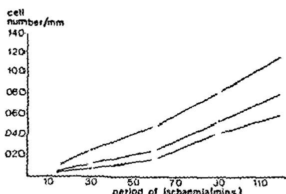


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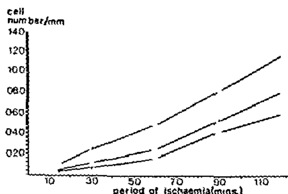


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POST MORTEM CHANGES IN THE RABBIT RETINA

A Study by Light Microscopy

BY

NEIL F JOHNSON and IAN GRIERSON

The course of post mortem changes in rabbit retina has been followed Short post mortem periods are accompanied by degenerative changes limited mainly to the visual cells and retinal pigment epithelium Long post mortem periods are associated with degenerative changes through out the retina Retinal tissue maintained at room temperature was less affected than that kept at body temperature (37 C) Post mortem changes are similar to those observed following periods of pressure induced ischaemia and it is thought that the mechanical effects of pressure on retinal tissue are minimal at the level of resolution afforded by light microscopy

Key words retina post mortem – ischaemia mechanical pressure effects

The course of post mortem changes in the rabbit retina has been followed Post mortem conditions are comparable to those prevailing after complete section of all the vessels supplying the eye In a previous investigation (John son 1974) complete retinal ischaemia has been studied by raising the intra ocular pressure sufficiently to abolish the flow of blood to the eye In this study the possible mechanical effects of pressure complicated the interpretation

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of ischaemic changes in the retina The present paper describes post mortem changes in the rabbit retina and draws a comparison between this tissue and the retinal tissue made ischaemic by high intraocular pressures in an attempt to determine the possible influence of pressure on the retina

Material and Methods

For this experiment 27 eyes from 18 adult Dutch rabbits were used The animals were sacrificed by an overdose of 40 % urethane administered via the marginal ear vein The eyes were enucleated and immersed in Dulbelcco s phosphate buffer at either 37 C or at room temperature The eyes were kept in this solution in the dark for either 15 30 60 90 or 120 min In three cases the eyes were enucleated and replaced in the orbit In a further group of animals the eyes were fixed immediately after enucleation The number of eyes used for the various experiments are shown in Table I

Following various post mortem periods the eyes were bisected in the equatorial plane and the two halves immersed in fixative at room temperature for at least four hours The fixative was 3 % glutaraldehyde buffered in Sorensen s phosphate buffer (pH 7 3) or 2 % glutaraldehyde buffered in 0 $^{\circ}$ M sodium cacocylate (pH 7 3–7 4) Following fixation retinal tissue was dis sected out from the area of the visual streak periphery and horizontal nerve fibre zone The dissection was carried out in a solution of 8 % buffered sucrose (Sorensen s phosphate buffer) After the dissection the tissue was

Table I
Table showing the number of animals investigated at the various post mortem periods

Post mortem period (min)	Room temperature	37°C
0 (control	–	4
15	3	2
30	3	2
60	2	2
90	3	2
120	2	2

conventionally prepared for electron microscopy 1 micron thick sections were stained with Loeffler s methylene blue followed by alcoholic differentiation for light microscopy

Results

Control tissue (Fig 1)

This tissue was similar in organisation to that described in normal rabbits by Davis (1929) and Sjostrand & Nilsson (1964)

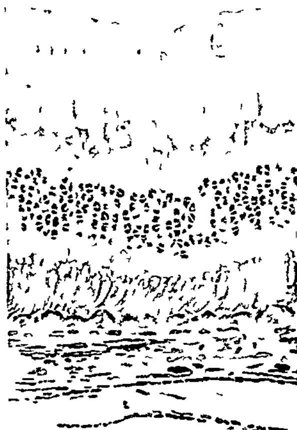


Fig 1
Light micrograph of the normal rabbit retina (× 850)

Post mortem tissue maintained at room temperature

In general short post mortem periods were accompanied by mild changes limited mainly to the visual cells while immediately after the longer post mortem episodes more marked changes were observed throughout the retina

In the retinal pigment epithelium vacuolation was evident following post mortem periods longer than 15 min The vacuolation initially involved small vacuoles in the basal region of the cell With long post mortem periods the vacuoles were larger and more widespread (Fig 4 a) In addition the apical surface of the pigment epithelium was often convexly distorted and the pigment granules were frequently distributed in a patchy fashion In spite of

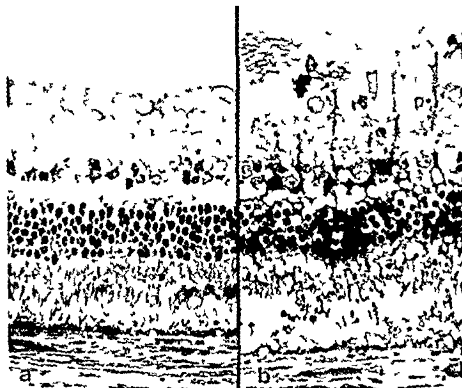


Fig 2

Light micrographs of the retina following various post mortem periods (room temperature)

a) 15 min post mortem The outer segments are disrupted the remainder of the retina is relatively normal (x 550)

b) 120 min post mortem The outer retina is severely damaged and there are also marked changes in the inner retina (x 550)

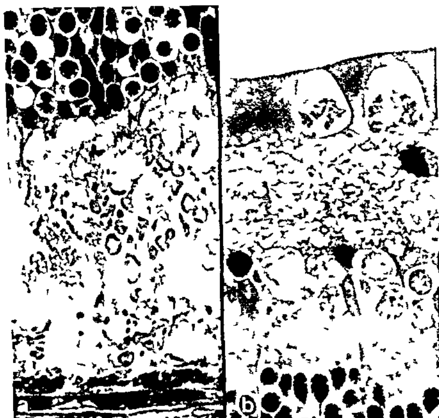


Fig 3

Light micrographs of the retina following 120 min post mortem (room temperature)
a) In the outer retina the inner and outer segments are disrupted and fragmented The visual cell nuclei are rounded and are often surrounded by a halo oedematous cytoplasm (x 1250)
b) Throughout the inner retina oedematous changes occur (x 1250)

the considerable disturbance seen in the pigment epithelium the cells remained intact and formed an uninteruppted covering of Bruch s membrane.

The changes in the retina 15 min post mortem were limited to the dis ruption of the terminal portions of the outer segments of the visual cells (Fig 2 a) With longer post mortem periods the disruption was more extensive There was fragmentation of the outer segments and in severe cases the frag ments formed swollen saccules (Fig 3 a) Following 120 min post mortem very little organisation was evident in the outer segments (Fig 2 b) In the inner

segments of the visual cells vacuolation occurred with post mortem periods longer than 15 min The vacuolation was more extensive with the longer post mortem periods The initial changes were in the ellipsoid region of the inner segment the myoid region appeared to have a greater resistance to



Fig 4

Light micrographs of the retina following 60 min post mortem (room temperature)

a) The myelinated nerve fibres and their associated blood vessels appear relatively normal (x 5>0)

b) In the outer retina macrophages occur adjacent to the retinal pigment epithelium (x 550)

change Both the ellipsoid and myoid regions were frequently fragmented after 90 and 120 min post mortem (Fig 3 a) With the varying periods following enucleation the inner segments appeared to be shorter than those of the control tissue

A prominent feature of the post mortem retina was the progressive accumulation of cellular debris in the sub retinal space with increasing post mortem periods The debris originated from the damaged inner and outer segments of the visual cells Accompanying this accumulation of debris were macrophages containing numerous darkly staining inclusion bodies These cells were found in all the groups of tissue studied and were commoner after the longer post mortem periods (Fig 4 b)

Changes in the outer nuclear layer were not immediately obvious after the shortest post mortem period the first signs of degeneration were observed 30 min after enucleation Pyknotic changes initially showed as rounding up of nuclei followed by loss of the normal chromatin pattern and a more intense staining reaction (Fig 3 a) The internuclear cytoplasm was often oedematous especially after long post mortem periods (60–120 min) These periods were in addition associated with the presence of microcystic spaces A constant feature was the better preservation of the nuclei of the cone cells compared with the rods The changes in the outer nuclear layer occurred uniformly throughout the retina

In the outer plexiform layer oedema was noticeable in the retinae subjected to post mortem periods longer than 30 min This was a generalised swelling which was more prominent with longer post mortem periods (Fig 2 b) The swelling could not be localised to any definite part of the layer Some processes and synaptic pedicles were distended while others were little affected

Post mortem periods longer than 30 min were accompanied by pyknotic changes in the inner nuclear layer The changes overall were less marked than those seen in the outer nuclear layer The nuclei stained less intensely and were more rounded than their counterparts in the control tissue these alterations were more marked 90 and 120 min post mortem (Fig 3 b) The changes in the nuclei were accompanied by oedematous alterations in the cytoplasm surrounding tehm The Muller cell nuclei appeared unaffected by even the longest post mortem period (120 min)

The inner plexiform layer behaved in a similar fashion to the outer plexiform layer showing a generalised swelling that was more pronounced with the longer post mortem periods

The ganglion cells were affected in a similar manner to the neural elements of the inner nuclear layer with oedematous changes in the cytoplasm and pale staining nuclei The intracellular oedema often created a translucent

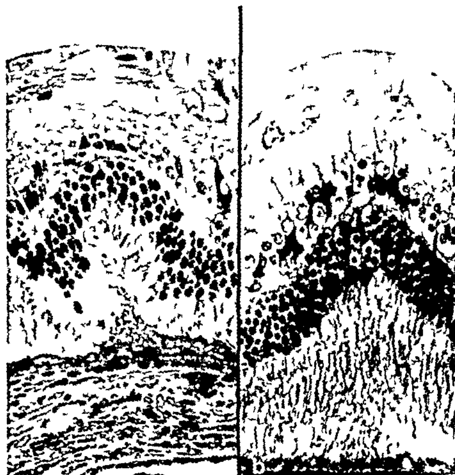


Fig 5
Light micrographs showing the retinal folding that accompanies post mortem periods
a) 90 min ischaemia The retinal folding is confined mostly to the outer layers of the retina (× 550)
b) 60 min post mortem (room temperature) The folding involves all the layers of the neural retina (× 550)

area in the periphery of the cell which was frequently associated with a condensation of the cytoplasm in the region of the nucleus (Fig 3 b)

The nerve fibre zone was also oedematous following post mortem periods longer than 60 min although no obvious changes were seen in the bundles of myelinated nerve fibres or their associated blood vessels (Fig 4 a)

In addition to these cellular changes the overall organisation of the retina was often disturbed With post mortem periods longer than 60 min folds in

the retina were often observed The folding generally involved the whole neural retina (Fig 5 a) although on occasion only the outer layers of the retina were involved (Fig 5 b)

Post mortem tissue maintained at 37°C

Degenerative changes observed in this group were similar to that seen in post mortem tissue maintained at room temperature although the alterations in the retina occurred more readily in tissue kept at 37°C 15 min post mortem was associated with disruption of the terminal regions of the outer segment in addition to mild vacuolation in the retinal pigment epithelium (Fig 6 a)



Fig 6

Light micrographs of post mortem retinal tissue maintained at 37°C

a) 15 min post mortem (× 550)

b) 60 min post mortem The changes are more marked in this strictly compared with the tissue maintained at room temperature (× 550)

30 min at 37°C resulted in tissue with a similar appearance to retinal tissue maintained at room temperature for 60 min with involvement of the inner retina 6–120 min post mortem at 37°C resulted in progressive retinal degeneration At 120 min post mortem the outer retina was disrupted with little evidence of any organisation in the inner or outer segments the pigment epithelium was undulating and heavily vacuolated The visual cell nuclei and those of the inner nuclei layer were severely pyknotic Pronounced oedema was evident in the outer and inner plexiform layer The ganglion cells had extensive intracellular oedema (Fig 6 b) A general feature of retinal tissue maintained at 37°C was the uneveness of the layers of the retina which was present within 30 min in addition to the widespread folding of the layers

Discussion

Following enucleation the rabbit retina is able to maintain its integrity for up to 15 min after which the retina shows degenerative changes Initially the damage is observed in the visual cells and retinal pigment epithelium

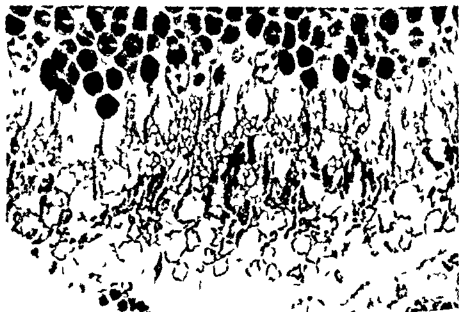


Fig 7

Light micrograph of the outer retina following 120 min pressure induced ischaemia The inner and outer segments are disrupted and fragmented This situation is similar to that seen in post mortem tissue (x 1750)

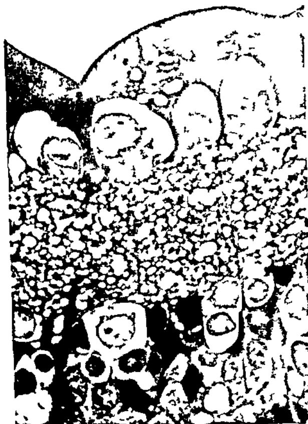


Fig 8

Light micrograph of the inner retina following 120 min pressure induced ischaemia The oedematous changes are similar to these observed in post mortem tissue (x 1250)

later there is involvement of the inner retina A feature of post mortem retinal tissue is the presence of mature macrophages in the sub retinal space These results are similar to those described in rabbits following section of the posterior ciliary arteries (Wagenman 1890 Nichols 1938) and complete ischaemia following elevated intraocular pressure (Johnson 1974) The rabbit retina is supplied entirely from the choroidal circulation as no true retinal circulation exists (Michelson 1954) This feature of the rabbit retina may account for the difference in the effect of complete ischaemia in animals with a dual circulation (Turnbull 1948 Smith & Baird 1952 Reinecke Kuwabara Cogan & Weis 1962 Levine & Ryan 1966 Fujino & Hamasaki 1967) In animals with a dual circulation the initial change was the occurrence of

oedema throughout the retina The oedema was more prominent in the inner retina and was followed by degeneration in the ganglion and bipolar cells with the eventual involvement of the whole retina

There is a striking similarity between post mortem tissue maintained at room temperature and tissue made ischaemic by high intraocular pressures (compare Figs 3 7 and 8) This similarity extends to all the layers of the retina even to the outer segments where one might expect to observe some deformation as a result of the high intraocular pressure employed to induce ischaemia This would suggest that the mechanical effects of pressure are minimal at the level of resolution afforded by light microscopy The effects of pressure would not appear to be a problem in the interpretation of ischaemic changes following periods of raised intraocular pressure Post mortem tissue may provide a good and convenient model for studying complete ischaemia although it does not allow recovery studies to be undertaken

Post mortem tissue maintained at body temperature has been observed to degeneration more readily than tissue kept at room temperature It has been shown that this latter tissue is remarkably similar to pressure induced ischaemic tissue in the intact animal This suggests that the temperature drop that must occur in the eye in the intact animal following complete ischaemia may prolong the period over which reversible structural changes can occur

Acknowledgments

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SPONTANEOUS CAROTID CAVERNOUS FISTULAS

Clinical Symptomatology

BY

GUDRUN BRISMAR and JAN BRISMAR

The symptomatology in six cases with spontaneous carotid cavernous fistulas is discussed All six patients presented with exophthalmos di lated veins pain and restriction of ocular movements In four patients a bruit was found objectively as well as subjectively four patients ex hibited an increase of the intraocular pressure and in three cases vision was impaired Of spe ial interest is the finding that discrete symptoms such as venous congestion and slight pain appeared early in the course of the disease in all patients and that in some of the patients an increase in intraocular pressure as well as disturbances in ocular motility were diagnosed long before the appearance of the exophthalmos

Key words carotid cavernous fistulas – cavernous sinus pathology – exophthalmos – glaucoma diagnosis – orbit pathology

Carotid cavernous fistulas may from aetiological viewpoints be divided int two categories cases in which the appearance of the fistula is related to skull trauma (traumatic fistulas) and cases without a history of an adequat trauma (spontaneous fistulas) According to previous investigators (Sattler 19?(Locke 1924 Henderson & Schneider 1958) the former category comprises abo 75 per cent of the cases Spontaneous fistulas are however being diagnosed wit

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increasing frequency probably as a result of the improved diagnostic possibilities offered by selective angiographic techniques

The aetiology of spontaneous carotid cavernous fistulas is not yet known Rupture of minor congenital aneurysms arteriosclerosis and congenital defects in the walls of the vessels are all possible explanations for fistulas between the internal carotid artery and the cavernous sinus (Dandy & Follis 1941 Walsh & Hoyt 1969) dural arteriovenous malformations have been suggested as expla nations for fistulas between external carotid artery branches and the cavernous sinus (Dilenge 1975)

The purpose of the following presentation of our personal material of spon taneous carotid cavernous fistulas is to demonstrate that the clinical sympto-matology may be discrete and that symptoms have often been present for a considerable period of time before the correct diagnosis is made or even sus pected

Material and Methods

The clinical material consists of six consecutive patients with spontaneous carotid cavernous fistulas draining into the orbital veins four women aged between 61–75 years one 49 year old man and one 13 year old girl with Down s disease All patients were radiologically examined with bilateral carotid angio graphy as well as with orbital phlebography The radiological findings in these patients have previously been presented in detail (Brismar & Brismar 19/6a) the cases in that report were designated with the same numbers All values of intraocular pressure were obtained by applanation tonometry

Case 1

A 69 year old previously healthy woman in November 19 1 experienced pains in the right parietal region below the right eye at the root of the nose and around the right ear In January redness and irritation of the right eye was also noted She consulted a physician and was treated for conjunctivitis In June 19 ? an increased intraocular pressure was found in the right eye (?9 mmHg) and the patient was hospitalized on the suspicion of glaucoma Shortly afterwards a right sided exoph thalmos of 6 mm with restriction of the ocular movements was found The patient at this time noticed a blowing sound in the right ear After exclusion of endocr ne aetiology of the proptosis she was referred to the University Hospital in Lund for further evaluation Ophthalm logical examination in August 19 _ re ealed a right sided pulsating exophthalmos with an objectively verif able bruit, an abducent ner e paresis and a partial ocul m tor nerve paresis The vision was norma' Neu ad o logical examination disclosed a right carotid cavernous fistula upplied from bilateral external and internal carotid artery branches and draining through the r ght super r

ophthalmic vein and also demonstrated changes indicative of a posterior right *cavernous sinus thrombosis*

The patient was treated with multiple transcutaneous catheter embolizations of external carotid artery branches to the fistula with excellent subjective results the pains and the bruit disappeared The objective findings (proptosis restriction of ocular movements increased intraocular pressure) however remained essentially unchanged

Case 2

A 63 year old woman previously healthy except for gonarthrosis developed a left sided frontotemporal headache in May 1973 One month later diplopia was also experienced Ophthalmological examination revealed a slight reddening of the right eye and partial right abducent and oculomotor nerve palsies A few weeks later following slight pains in the right eye and a sound sensation like the sound of birds wings in the right ear a right sided exophthalmos appeared On examination, on *the right side in addition to the previously observed eye muscle palsies a 5 mm* exophthalmos was found as well as chemosis and signs of both external and internal stasis One month later a left sided abducent nerve paresis became apparent Intraocular pressure and visual acuity were bilaterally normal during the entire period of observation

The patient was referred for neuroradiological evaluation on the suspicion of either an arteriovenous fistula or an intraorbital tumour on the right side Bilateral carotid angiography orbital phlebography and phlebography of the inferior petrosal sinus demonstrated a carotid cavernous fistula supplied from left and right external as well as from left internal carotid artery branches The fistula drained exclusively through the left superior ophthalmic vein Thrombotic changes were found in the right superior ophthalmic vein and cavernous sinus as well as in adjacent basal sinuses of the skull

On examination in January 1974 the symptoms and signs had almost completely disappeared without any treatment

Case 3

A 13 year old institutionalized severely mentally retarded girl with Down s disease in *the summer of 19 3 was found to have a reddened right eye interpreted as con*junctivitis In November 1973 a right sided proptosis as well as limitations of movements of the right eye was noted and in January 1974 the patient was hospitalized with a suspected intraorbital tumour

Ophthalmological evaluation was difficult as the patient was unable to cooperate but revealed no pathological findings on the left side On the right side a slight exophthalmos and restriction of ocular movements were verified A moderate external venous stasis most pronounced temporally was found and the retinal veins were widened and tortuous The intraocular pressure judged to be normal by palpation As skull films demonstrated a soft tissue mass in the right maxillary sinus this sinus was at first explored to exclude a tumour However no tumour was found and the patient was referred for neuroradiological evaluation Right selective internal and external and left common carotid angiographies as well as orbital phlebography dis

closed a right sided carotid cavernous fistula solely supplied from the accessory menin geal branch of the right maxillary artery

The patient was not subjected to any treatment and six months later signs per sisted unchanged

Case 4

A 48 year old man with a history of operated and healed pulmonary tuberculosis in September 1973 suffered from influenza with occipital headache diarrhoea and fatigue Fourteen days later he noticed reddening of the right eye proptosis fol lowed a few days later and he was referred to an ophthalmological clinic under the diagnosis of a possible acute glaucoma An ophthalmological examination demon strated an increased intraocular pressure (37 mmHg) and decreased visual acuity (3/10) on the right side while the left eye was normal The patient was hospitalized with a suspected intraorbital phlegmon or tumour

Eight days after admission the right sided exophthalmos as well as the periorbital swelling and the chemosis rapidly increased The patient developed severe right sided orbital pains and ocular pulsations became apparent The visual acuity in the right eye decreased to discrimination of hand movements A right common carotid angiography disclosed a carotid cavernous fistula probably caused by rupture of an intracavernous right internal carotid aneurysm draining solely through the right superior ophthalmic vein. A right middle cerebral artery aneurysm was also found Left carotid angiography two weeks later was normal Ophthalmological examination at that time demonstrated on the right side a 13 mm protrusion of the bulb total ophthalmoplegia an oedematous cornea with decreased sensibility and a constriction of the visual field (confrontation method) which was most pronounced nasally

One month later a right carotid angiography demonstrated unchanged findings and an occlusion of the fistula with a Fogarthy balloon catheter was att mpted The patient however developed ischemic symptoms on inflation of the balloon and the balloon had to be withdrawn immediately The symptoms and signs spontaneously decreased during the subsequent months (visual acuity in the right eye improved to 5/10 the intraocular pressure and the visual field (Goldmann) returned to normal) A control angiography three months after the attempted balloon occlusion showed closure of the fistula but persistent filling of an intracavernous carotid aneurysm

A further 3 months later the proptosis had completely disappeared and the visual acuity in the right eye increased to 6/10–7/10 A slight ptosis was still present and the right pupil was larger than the left

Case 5

A 61 year old woman with a two year history of a left sided glaucoma was sub jected to a fistulating operation in 1974 (sclerectomy and iridencleis) as conservative therapy had failed to control the intraocular pressure Visual acuity and fields were bilaterally normal prior to operation Preoperatively as well as postoperatively quite pronounced venous injection of the conjunctiva was present Three weeks after opera tion the patient developed pains chemosis periorbital oedema and proptosis on the left side The venous injection also increased Ophthalmological examination a further

three weeks later demonstrated in addition an abducent nerve paresis on the left side and dilated veins with small haemorrhages in the left retina

Orbital phlebography was performed to exclude a retro orbital haemorrhage and the findings suggested the possibility of a carotid cavernous fistula A left sided carotid angiography confirmed this diagnosis by demonstrating a fistula fed by the left internal carotid artery and drained through the left superior ophthalmic vein

Two and a half months after the operation the left sided exophthalmos measured 5 5 mm the intraocular pressure amounted to 28 mmHg and the vision had decreased to discrimination of hand movements A left sided ptosis was also found and the left visual field showed irregular temporal as well as nasal defects

Two weeks later a repeat orbital phlebogram as well as a right carotid angiography demonstrated spontaneous healing of the fistula resulting from occlusion of the left superior ophthalmic vein The clinical symptoms and signs rapidly improved and on discharge one week later the visual acuity bilaterally was 1 0 and the intra ocular pressure was bilaterally normal (right 15 left 19 mmHg) A slight left sided proptosis and abducent nerve palsy was however still present

Case 6

A 75 year old previously healthy woman in September 1974 noted reddening of the right eye and a bubbling sensation in the right ear One month later an ophthalmologist diagnosed conjunctivitis After a further three weeks a right sided 5 mm exophthalmos suddenly appeared the bubbling at the same time increased to an constant pulse synchronous bruit Ophthalmological examination disclosed an increased intraocular pressure on the right side (35 mmHg) The function was bilaterally normal except for a right sided homonymous partial hemianopsia that remained unchanged during the entire course of the disease and was therefore interpreted as an accidental finding

Orbital phlebography demonstrated findings compatible with a carotid cavernous fistula draining through the right superior ophthalmic vein In addition a wall attached thrombus was observed in the right superior ophthalmic vein and thrombotic changes were also present in the basal veins of the skull

After a right inferior petrosal sinus phlebography performed to further evaluate the thrombotic changes at the skull base the right sided symptoms dramatically increased indicating widening of the fistula (Brismar et al 1976b) The exophthalmos increased to 9 mm total ophthalmoplegia and ptosis developed the corneal sensibility decreased slightly the intraocular pressure increased further and the vision was impaired to discrimination of hand movements A pronounced external venous stasis with lid swelling and a slight internal venous stasis was also found Arteriographic examinations disclosed a carotid cavernous fistula supplied from right external and internal carotid artery branches and draining into the right superior ophthalmic vein The symptoms and signs then successively decreased when an acute right iridocyclitis complicated the course – this disease however healed (leaving some posterior synechias) after medical treatment At an ophthalmological examination in January 1975 the right proptosis had decreased to 4 mm the periorbital swelling had disappeared and the vision in the right eye had increased to 3/10 The intraocular pressure on the right side however measured 40 mmHg in spite of treatment with miotic drugs

Discussion

Traumatic carotid cavernous fistulas are most frequently found in the most active age groups (Henderson & Schneider 1958 Madsen 1970) On the other hand spontaneous fistulas have been reported to have a prevalence for women of upper middle age (Walsh & Hoyt 1969) This is also the case in our material where four out of the six patients were women between 61–75 years of age The two remaining cases differed not only in age or sex in the male an intra cavernous carotid aneurysm was the probable cause of the fistula and in the child the concomitant presence of Down s disease and a cardiovascular malfor mation suggested a congenital origin of the fistula

Traumatic carotid cavernous fistulas are much more common than spon taneous fistulas and thus dominate most reports concerning the symptomatology of fistulas The symptoms and signs in spontaneous fistulas however seem to be the same though they are often far less pronounced (Sanders & Hoyt 1969)

Some degree of exophthalmos was found in all our patients and has also been a frequent finding in previous reports on spontaneous fistulas (Newton & Hoyt 1970 Taniguchi et al 1971) The degree of exophthalmos has usually been moderate In our material the ophthalmometric differences between the two eyes ranged from 5 5 to 13 mm

The existence of a contralateral proptosis observed in our Case 2 may be explained by thrombotic changes occluding the primary drainage routes of the fistula (Dandy & Follis 1941 Bynke & Efsing 1970 Taniguchi et al 1971 Brismar & Brismar 1976a) thereby forcing the fistula to drain through the contralateral orbit via normally existing connections between the two cavernous sinuses

Pulsating exophthalmos has classically been regarded as a cardinal symptom of carotid cavernous fistulas but in most materials is not very frequent Madsen (1970) however reported a rate as high as 15/18 patients but also included cases in which the pulsations were only detectable under slit lamp

Bruit is the second classical cardinal symptom of a carotid cavernous fistula and seems also to be an important symptom in spontaneous fistulas (Taniguchi et al 1971 Newton & Hoyt 1970 Table I) The bruit may initially be very discrete and some of our patients had difficulties in describing it as well as in appreciating its pulse synchronous character The bruit may as in our patient 6 present as the primary symptom and significantly preceed the de velopment of exophthalmos (Rosenbaum et al 1969 Taniguchi et al 1971 Rainer & Haselbach 1975) In the remaining three patients in our material the bruit appeared at the same time as the exophthalmos

A restriction of ocular movements may not only be caused by an affection

Table I

Ophthalmological findings in carotid cavernous fistulas

	Henderson & Schneider	Madsen	Stolpmann	Newton & Hoyt	Taniguchi et al	Present material
Traumatic/Spontaneous	14/3	16/2	0/2	1/10[1]	0/11[2]	0/6
Females/Males	7/10	5/13	2/0	8/3	8/3	5/1
Exophthalmos	17/17	17/18[3]	2/2[4]	10/11	8/11	6/6
Of those pulsating	5	15	1	0 (?)	0 (?)	2
Bruit	15/17	17/18	1/2	6/11	9/11	4/6
Pains	15/17	?	1/2	10/11	3/3	5/5
Palsies totally	?	18/18[5]	2/2	7/11	6/11	6/6
N III	7/17	2/16	1/2	0/11	3/11	5/5
N IV	6/17	1/16	0/2	0/11	0/11	2/5
N V	5/17	3/16	0/2	0/11	0/11	2/5
N VI	10/17	7/16[6]	2/2[4]	7/11	3/11	5/5[6]
Increased intraocular pressure	7/17	4/4	2/2[4]	5/11	5/7	4/6
Reduced visual acuity	9/17	12/15[7]	0/2	2/11	?	3/5
Lid swelling	8/17	18/18[3]	1/2[4]	?	?	3/6
Dilated conjunctival veins	15/17	18/18[3]	2/2[4]	10/11	9/11	6/6
Dilated retinal veins	13/17	11/17	2/2[4]	?	?	5/6
Papillary oedema	0/17	4/17	0/2	?	?	0/6

[1] Only 10 cases draining through the orbital veins [2] Only 6 cases draining through the orbital veins [3] Bilaterally in four cases
[4] Bilaterally [5] 6 patients (2 unconscious) without any eye movements (in 2 cases bilaterally) in 4 patients impaired movements
[6] Bilaterally in one cases [7] 2 of these bilaterally no light perception

of the motor nerves of the eye but also by mechanical effects from venous congestion and oedema In cases with pronounced exophthalmos and total ophthalmoplegia a differentiation between the two causes is not possible The eye muscle nerves most frequently affected are the abducent and oculomotor nerves Affection of other cranial nerves is less frequent However in two patients in our material (Case 4 Case 6 after the skull base phlebography) reduced corneal sensibility was found

Different explanations for the cranial nerve involvement have been suggested Dandy & Follis (1941) presented one autopsy case with a well defined round herniation of the cavernous sinus beneath the third nerve which was markedly flattened by it as if by a tumor Nerve palsies may also be caused by impairment of the blood supply to the nerves (Newton & Hoyt 1970)

Pain is one of the most frequently described symptoms in association with carotid cavernous fistulas and may lead to the initial clinical diagnosis of migraine (Newton & Hoyt 1970 Taniguchi et al 1971) The pains may be localized to the orbit the root of the nose the temple the forehead or the parietal region and may be of different intensity Those patients who had the most severe pains in our material (Cases 4 6) in other respects also presented with the most pronounced symptoms and signs The remaining three patients experienced only moderate pains

Conjunctival injection was the first symptom in four of our patients in two of them as a single symptom and in two associated with slight pains All four patients were interpreted by physicians as having a conjunctivitis and treated with eye drops This misinterpretation has also been reported by other investigators (Stolpmann 1973 Newton & Hoyt 1970) Corkscrew tortuosity and a bright red hue of the epibulbar venous plexus have been emphasized as striking diagnostic signs (Henderson 1973) but were not noticed in any of our cases The time interval between the first signs of external stasis and the appearance of more significant signs was variable in our material but at most (Case 3) amounted to 3 months

Signs of retinal venous congestion is a common finding and was present in 5 of our patients These signs may be subtle and are easily overlooked (Sanders & Hoyt 1969) Papillary oedema is rare and was neither found in our material nor in the material of Henderson & Schneider (1958) Madsen (1970) described a blurred disc in 6/18 cases and Mingrino & Moro (1967) presented one case with papillary oedema

Chemosis was found in four out of six patients in our material in three of them combined with lid swelling Henderson & Schneider (1958) found chemosis in 6/17 patients

Reduced visual acuity is an important symptom in carotid cavernous fistulas

and as the threat to life is small in this condition preservation of vision becomes the major aim of therapy (Sanders & Hoyt 1969) In our material three patients (Cases 4 5 6 following skull base phlebography) had a pronounced impairment of vision all of whom also had a rapid progression of exophthalmos and pronounced other symptoms The vision improved following closure of the fistula In the three patients with slowly progressive symptoms (Cases 1 3 *as well as Case 6 before phlebographic examination) no impairment* of vision was found This is consistent with the experiences of other authors (Stolpmann 1972 Rainer & Haselbach 1975) Sanders & Hoyt (1969) suggested that the cause of visual failure in carotid cavernous fistulas is hypoxic changes produced by a decreased perfusion pressure

Visual field defect in the form of nasal as well as temporal restrictions were temporarily seen in two of our cases (Cases 4 5) in association with the reduction of visual acuity – in both cases the defects disappeared when the vision improved

Secondary glaucoma is a well known complication of carotid cavernous fistulas The increase in pressure has usually been reported as moderate (up to about 30 mmHg) and has been related to the increased episcleral venous pressure (Sanders & Hoyt 1969) Cases exhibiting a dramatic increase in pressure have however also been described (Burton & Goldberg 1970 Stolpmann 1972 Muhlbacher & Hanselmayer 1973) Henderson & Schneider (1958) in a review of previous materials found the reported frequency of glaucoma to vary between 6 7–31 % Zozulia & Burlutsky (1970) found glaucoma in 24/50 patients In our material the pressure was increased in 4/6 patients in two the increase was related to the appearance (Case 4) or rapid increase (Case 6) of the exophthalmos and in two it preceded the other symptoms One patient (Case 1) was thus initially hospitalized for the evaluation of a possible glaucoma the other (Case 5) had been treated for glaucoma for two years and had been subjected to a fistulating operation 3 weeks prior to the onset of exophthalmos A similar case was presented by Henderson (1973) In one of the cases of Taniguchi et al (1971) and in several cases of Newton & Hoyt (1970) the initial clinical diagnosis was that of glaucoma

In two of our patients in whom the fistula closed the pressure spontaneously normalized in the two other patients in whom the fistula clinically at least partially persisted the intraocular pressure was still increased at the time of the last followup in one of them in spite of local therapy

Experiences from this material as well as from previous series of spontaneous fistulas (Rosenbaum et al 1969 Newton & Hoyt 1970 Taniguchi et al 1971 Grunert et al 1972 Stolpmann 1972 Rainer & Haselbach 1975) demonstrate that the time interval between the appearance of the first symptom (and even

symptoms and signs that in retrospect seem clearly to indicate the presence of a fistula) and the establishing of the correct diagnosis is often considerable

The time period between the onset of symptoms and the correct diagnosis in our material was 2 years (if the glaucoma in Case 5 is considered secondary to the fistula) in one patient 8 months in one 6 months in another 3 months in 2 patients and 3 weeks in the last patient This last patient however had an aneurysm and a more dramatic onset of symptoms than is normally seen in spontaneous fistulas

As evident from the present material as well as from the literature the spontaneous fistulas have a large tendency to close spontaneously or following non surgical procedures such as angiography (Newton & Hoyt 1970 Taniguchi et al 1971) Surgical intervention is according to Sanders & Hoyt (1969) not even motivated in cases with traumatic fistulas as the preoccupation with improved methods to direct trap or obliterate the fistula has increased the morbidity and mortality of the disease without reducing the incidence or severity of visual deterioation The development of percutaneous trans catheter embolization techniques however justifies a modification of this statement and it seems reasonable to try to embolize all the external carotid feeders that can be attacked without significant risk

Conclusions

The symptoms and signs of spontaneous carotid cavernous fistulas are often very discrete and may propagate for a long time before the correct diagnosis is established

The presence of a spontaneous carotid cavernous fistula should be suspected when a slight unilateral conjunctival injection especially if associated with ipsilateral headache persists for a long time in spite of adequate therapy for conjunctivitis

This diagnosis should also be considered in cases with unilateral therapy resistant glaucoma in which no other causative factor is found

Subjective sound sensations not necessarily experienced as either pulse synchronous or as a bruit are often present in spontaneous carotid cavernous fistulas As these symptoms are often very mild a direct question may be necessary in order to disclose them

As therapy seldom hastens in these cases there is however no indication for angiographic examinations (which carry a significant risk for complications) just to disclose a minor fistula in cases with slight uncharacteristic symptoms and signs

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PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

Evidence for a Generalised Mitochondrial Disease with a Defect in Pyruvate Metabolism

BY

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Muscle biopsies from four patients with chronic progressive external ophthalmoplegia and pigmentary retinopathy with symptoms and signs from other organs were studied by means of light and electron microscopy Examination revealed a marked proliferation of abnormal mitochondria with a degeneration of both muscle and nerve tissue Blood levels of lactate and pyruvate were measured and abnormal values of these metabolites were found in the three patients with the most pronounced ultrastructural changes On the basis of these findings it is suggested that there is a biochemical defect in pyruvate lactate metabolism which could be responsible for the marked proliferation of the abnormal mitochondria

Key words ophthalmoplegia plus – muscle biopsy – abnormal mitochondria – metabolic defect – blood pyruvate – blood lactate.

Chronic progressive external ophthalmoplegia was originally considered to be a disease primarily affecting brain stem nuclei as first described by von Graefe (1866) However Kiloh & Nevin (1951) were able to demonstrable histopatho

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logical changes in the extraocular muscles and concluded that the disorder was due to a myopathy The neural changes reported in earlier studies were regarded as inconclusive This view has prevailed in the majority of subsequent studies (Schwarz & Liu 1954 Beckett & Nersky 1953 Kearns & Sayre 1958 Cogan et al 1962 Lind & Prame 1963) Koerner & Schlote (1972) stated that there was not enough evidence to consider chronic progressive external ophthalmoplegia as part of an entity of neurogenic disorders

However it has become increasingly difficult to explain chronic progressive external ophthalmoplegia as being purely and simply a myopathy of the extra ocular muscles Involvement of other facial muscles limb musculature cerebellum spinal tracts myocardium endocrine glands hearing and probably most frequent of all retina with pigmentary changes and chorioretinal atrophy has amply been described in the recent literature (Alfano & Berger 1957 Kearns & Sayre 1958 Jager et al 1960 Drachman 1968 Rosenberg et al 1968 Daroff 1969 Lowes 1975) Endocrine abnormalities have been reported by Lundberg (1962)

Abnormal mitochondria in muscle tissue have been demonstrated by Gonatas (1967) Mair & Tomé (1972) Morgan Hughes & Mair (1973) Iannaccone et al (1974) and Schlote & Korner (1976)

In a preliminary report by two of the authors (Lou & Reske Nielsen 1976) a biochemical defect in pyruvate lactate metabolism in three of the patients involved in the present study has been suggested The purpose of the present study is to report on the ultrastructure of muscle biopsies in four cases of progressive external ophthalmoplegia and to attempt to correlate the findings with the proposed metabolic defect in pyruvate metabolism

Material and Methods

The material comprised four patients two male and two female aged from 13–50 years The patients all had a chronic external ophthalmoplegia and pigmentary retinopathy with a variety of associated disorders including cardiac conduction defects endocrine disturbances and central nervous system involvement The main points from the case histories are summarized in Table I Muscle biopsies were taken from the left deltoid muscle in cases 1 2 and 3 In the fourth case biopsies were taken from the right superior rectus muscle the right levator palpebrae muscle and the left deltoid muscle The biopsies were taken and prepared for histological examination as described by Reske Nielsen et al (1969) The muscle specimens for electron microscopy were fixed in 2 % glutaraldehyde for approximately 3 h and 1 % osmium tetroxide for

Table I
Summary of the case histories

Cases	1	2	3	4
Age on presentation (years)	50	23	17	25
Sex	M	M	F	F
Ptosis and ophthalmoplegia	+	+	+	+
Pigmentary retinopathy	+	+	+	+
Cardiac conduction defects	+	+	0	+
Cardiac complaints	+	0	0	+
Cardiac pacemaker	–	–	–	+
Frail build	+	–	+	+
Low average intelligence	–	–	–	+
Deafness	+	0	0	+
Facial weakness	+	+	+	+
Secondary sexual abnormalities	+	+	+	+
Abnormal electroencephalography	+	+	+	+
Abnormal electromyography	+	–	0	0
Abnormal electroretinography	–	0	+	+
Abnormal colour vision	0	–	+	+
Abnormal dark adaptation	0	+	–	+
Enlarged blind spot	+	–	–	+
Elevated CSF protein	0	0	0	+
Asymptomatic diabetes	+	0	0	+
Raised Se cholesterol	–	–	–	–
Raised Se lactate dehydrogenase	0	+	–	+
Raised Se aldolase	0	–	–	–
Raised Se creatine phosphokinase	0	–	–	–

Key + present – absent 0 not recorded

one h then dehydrated with increasing alcohol concentrations (24 % up to 99 %) and anhydrous acetone and finally embedded in Vestopal W. Six grids from each of five blocks from each specimen were examined. The grids were stained with uranyl magnesium acetate and lead citrate and examined in a Zeiss EM 9 (Reske Nielsen & Harmsen 1972).

Electromyography was performed in cases 1 and 2 in the right deltoid muscle.

In addition data on blood pyruvate and lactate concentrations were obtained. In three cases the method used for the estimation was that described by Lundholm et al. (1963). In the remaining case the method described by Marbach & Weil (1967) was used. These findings are shown in Table II.

Table II

Blood concentrations (mmol/l) of pyruvate and lactate

Method Lundholm et al (1963)

	Pyruvate (normal range 0.035–0.139) (SD 0.04)	*Lactate* (normal range 0.55–1.75) (SD 0.01)
Patient 1 (rest)	0.160	2.58
(rest)	0.143	2.28
(moderate exercise)	0.191	4.85
Patient 2 (rest)	0.059	1.59
Patient 3 (rest)	0.137	2.57
(rest)	0.108	1.99
(moderate exercise)	0.152	3.62

Method Marbach & Weil (1967)

	Pyruvate (normal range 0.02–0.08)	*Lactate* (normal range 0.695–1.67)
Patient 4 (rest)	0.135	1.55
(rest)	0.15	2.55

Results

Case 1 A 50 year old male business executive who underwent an operation for strabismus at the age of 7 years A left deltoid muscle biopsy was examined by the Department of Neurophysiology Rigshospitalet

Light microscopy Increased number of internal nuclei Several necrotic and basophilic fibres In about 20 % of the fibres excessive amounts of subsarcolemmal material (probably mitochondria) were present which stained dark with lactate dehydrogenase and bright red with Gomori's trichome stain

Electron microscopy The cross striation of the myofibrils was well preserved but out phase in many fibres Central myonuclei and the number of satellite cells were increased Some fibres contain subsarcolemmal accumulations of mitochondria Intramitochondrial crystals were abundant

Case 2 A 23 year old male metal worker who developed ptosis of both eyes around the age of 14 years A biopsy from the left deltoid muscle was examined

Light microscopy A few abnormal muscle fibres which appeared red and granular with Gomori's trichome stain Histochemistry was not performed

Electron microscopy Accumulations of mitochondria were seen close to the nucleus beneath the sarcoplasma membrane Some showed abnormal cristae and vacuoles Electron dense granules presumably glycogen granules were present No paracrystal line inclusions could be demonstrated Lipid vacuoles were seen between the myo fibrils Some myofibrils were atrophic and disorganized with spiky and flowing Z membranes

Case 3 A 17 year old schoolgirl who developed a gradually progressive bilateral ptosis at the age of 8 years A biopsy was taken from the left deltoid muscle

Light microscopy Several fibres in each fasicle contained loosely structured muscle fibres These were granular and red stained with Gomori s trichrome stain Further more many basophilic muscle fibres with occasional necrotic fibres were seen Histo chemistry was not performed

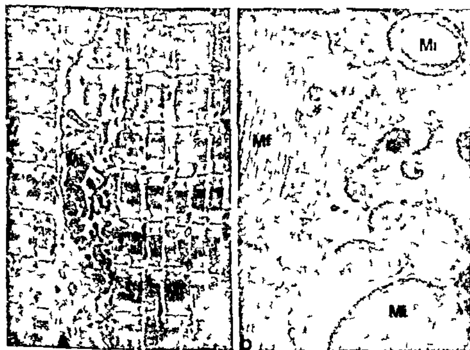


Fig 1

a Ultrastructure of the left deltoid mus le showing subsarcolemmal aggregations of abnormal mitochondria (Mi) and thinning of the myofibrils (Mf) Longitudinal section 6000 (Case 3 EM 597)

b Electron micrograph revealing large mitochondria (Mi) partly or totally filled by concentrically arranged membranes Longitudinal section ×2 000 (Case 3 EM 597)


Cr
Va
G
S

Electron microscopy The dominating feature was an abnormality of the mitochondria There were large aggregates of mitochondria beneath the sarcolemma and between the myofibrils The size of the mitochondria varied considerably and many giant mitochondria were present The configuration was also variable and many bizarre forms were seen The external membrane was double or triple and in some cases contained even more layers The cristae were often absent or transversed the mito chondria Some mitochondria were filled out by thin concentrically arranged mem branes often with two centres Others had paracrystalline laminated inclusions and vacuoles with a single or double limiting membrane The vacuoles were either empty or contained myelin bodies or electron dense granules Furthermore some mitochondria contained tubular inclusions Glycogen granules were abundant Many giant mito chondria with a double limiting membrane were distended by closely packed electron dense granules Between the mitochondria glycogen granules and lipid droplets were present In addition many fibres were atrophic or even disrupted and the basal mem branes were folded The sarcotubular system as well as the vessels were normal (Figs 1 a 1 b and 2)

Case 4 A 25 year old woman who developed ptosis of both eyes around the age of 10 years This case has previously been published in Acta ophthal (Kbh) (Lowes 1975) and shows all the characteristics of the foregoing patients to a marked degree Three muscle biopsies were taken – one from the right rectus superior muscle one from the right levator palpebrae muscle taken at the time of operation for ptosis and one from the left deltoid muscle The ptosis operation has proved cosmetically successful with no exposure defect on closure

Light microscopy of superior rectus (Neurop No 19131) The scanty material con sisted of connective tissue with no inflammatory infiltration There were a few muscle fibres of varying diameter but without any degenerative changes With Gomori s trichrome staining shiny red granules were observed between the myofibrils Enzyme histochemistry was not performed (Fig 3 a 3 b)

Electron microscopy of superior rectus The muscle fibres and fibrils were small as a result of a loss of myofilaments The Z lines showed an extremely variable pattern with abnormally thin thickened, spiky and flowing lines Areas of muscle tissue were occasionally seen which had either disappeared or revealed contraction clumps Folded and empty basement membranes could also be seen The connective tissue was increased The most striking ultrastructural changes were large aggregations of mitochondria These were situated under the sarcoplasma membrane either close to the nucleus or between the myofibrils The mitochondria were much larger than nor mal and had an extremely varied appearance (Fig 3 c 3 d)

Some of these organelles were rounded possessing a single double or triple mem brane Others had a bizarre club shaped appearance They were either empty or contained an electron dense material Occasionally both vacuoles and granules were

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Fig 2

Left deltoid muscle Giant mitochondrion with abnormally arranged cristae (Cr) vacuoles (Va) and glycogen material (G) On the left a sarcomere (S) can be seen Longitudinal section × 90 000 (Case 3 EM 59)

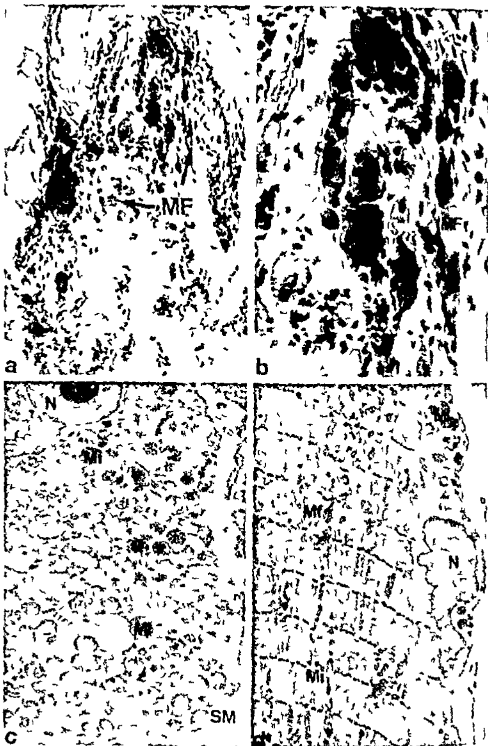


Fig 3 a b c d
(See text p 561)

found in the same mitochondrion The cristae generally had an abnormal arrangement with numerous concentric circles inside the organelles Certain of the mitochondria appeared normal in one part but abnormal in the other part In the giant mitochondria a variable number of laminated crystal like inclusions could be seen within the cristae The configuration of the laminated material depended on the plane of sectioning The mitochondria often contained lipid bodies and glycogen granules Lipid bodies were also seen in close proximity to the mitochondria (Figs 4 a 4 b 5 a 5 b) Two end plates were successfully demonstrated The axon the primary and the secondary synaptic clefts were morphologically normal The subneural apparatus which is limited by the muscular sarcoplasmal membrane contained numerous large closely packed, abnormal mitochondria which displaced the secondary synaptic clefts (not illustrated)

Light microscopy of levator palpebrae (Neurop No 20843 prep 3) The biopsy consisted of connective tissue with a few blood vessels and a scanty lymphocyte infiltration In the connective tissue there were occasional small groups of muscle fibres

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Fig 3

a Light microscopy of the right superior rectus muscle showing muscle fibres (MF) in cross and longitudinal sections separated by connective tissue × 40 (Case 4 LM 19131)

b Higher magnification of Fig 3 a × 100

c Electron micrograph of right superior muscle Large collections of mitochondria (Mi) under the sarcoplasma membrane (SM) close to the nucleus (N) × 6000 (Case 4 EM 633)

d Thin myofibrils (Mf) with abnormal mitochondria (Mi) in the interspaces Longitudinal section × 6000

Fig 4

a Right superior rectus muscle Accumulation of bizarre and enlarged mitochondria (abn Mi) under the folded sarcoplasma membrane (SM) Lipid bodies (LB) can be seen Longitudinal section × 27 000 (Case 4 EM 633)

b Mitochondria showing a varied appearance with an abnormal internal structure (Mi) between thinned out myofibrils (Mf) Longitudinal section × 2 000 (Case 4 EM 633)

Fig 5

a Right superior rectus muscle showing an area below the nucleus (N) which contains remnants of myofibrils (Mf) with laminated mitochondria (Mi) and lipid bodies (LB) Longitudinal section × 27 000 (Case 4 EM 633)

b Bulging of the sarcoplasma membrane (SM) which contains large abnormal mitochondria (abn Mi) with a complex arrangement of the cristae Longitudinal section × 27 000 (Case 4 EM 633)

Fig 4 a b
(See text p 561)

Fig 5 a b

(See text p 561)

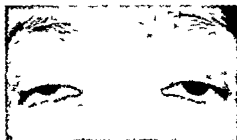


Fig 6

a Close up of the adnexal region showing the marked ptosis (Case 4)

b Biopsy from the right levator palpebrae muscle Light microscopy shows connective tissue (CoT) and fat cells (FC) No recognisable muscle fibres ×100 (Case 4 LM 20813 prep 3)

(maximum 3–4) with a rounded appearance and an intense stain with haematoxylin eosin Gomori's trichrome stain was inconclusive The small nerve branches were totally demyelinated and contained only a few degenerated nerve fibres Histochemistry was not performed (Fig 6 a 6 b)

a

Mi

b

Mi

Mi

Fig ? a b

(See text p 566)

Electron microscopy of levator palpebrae All the micrographs revealed normal blood vessels but with marked pinocytosis and considerable connective tissue Abnormal mitochondria were occasionally observed in the cytoplasma of fibroblasts Some of the mitochondria were empty but in others an abnormal arrangement of the cristae could be observed (Fig 7 a b)

The preparation contained no recognisable muscle tissue

Light microscopy of deltoid muscle (Neurop No 20543 prep 1) Skin from the deltoid region examined by conventional technique was normal Gomori s trichrome stain was inconclusive Electron microscopy was not performed Muscle fibres with a granular structure and single basophilic fibre segments were found in all fascicles No necrotic fibres were observed In the modified Gomori trichrome stain almost every muscle fibre, especially the granular type contained bright shiny red granules These granules were either confined to the subsarcolemmal regions or formed a coarse punctate pattern over the entire cross sectional area of the fibre There was an increase in the number of nuclei and these were occasionally centrally placed

Frozen sections An intense staining of the intermyofibrillary structures was a striking feature of the haematoxylin eosin staining These fibrillary structures displayed a coarse reticular pattern when compared with normal material

Numerous small lipid droplets stained by Scharlach Rot were seen in cross section of the muscle fibres On histochemical examination the same areas were intensely stained with DPNH tetrazolium reductase and could be seen as abnormal deposits in the subsarcolemmal regions and over the entire cross sectional area of the fibres ATPase demonstrated an absence of myofibrillary material in the affected regions of

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Fig 7

a Right levator palpebrae muscle Mitochondria (Mi) containing abnormal cristae are to be found in the cytoplasm of a fibroblast × 27 000 (Case 4 EM 751)

b Higher magnification of Fig 8 b × 81 000

Fig 8

a *Left deltoid muscle Light microscopy (frozen section) with an intense staining of the intermyofibrillary structures The nuclei are marked by circles* (Haematoxylin eosin) Cross section × 400 (Case 4 LM 20843 prep 2)

b Histochemical preparation (DPNH) Both type 1 and type 2 muscle fibres are shown Mitochondrial enzymes are visualised as abnormal deposits under the sarcoplasma (marked by circles) and as a coarse network over the entire cross section in both types of fibres × 400

Fig 9

a Left deltoid muscle Section demonstrating the giant and peculiar mitochondria (Mi) with numerous crystalline inclusions sectioned in various planes Longitudinal section × 27 000 (Case 4 EM 756)

b Fingerprint like configuration of mitochondria (Mi) lying between two myofibrils (Mf) Longitudinal section 97 000

Fig 8 a b
(See text p 566)

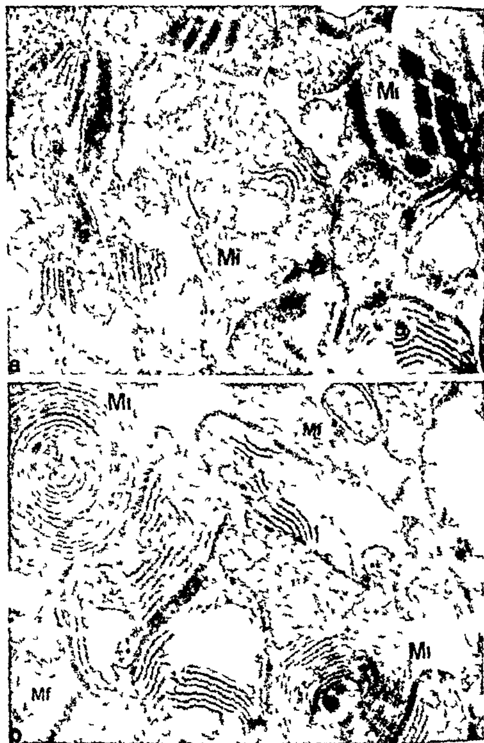


Fig 9 a b
(See text p 566)

the muscle The biopsy material showed a normal mosaic pattern of the type 1 and type fibres Both histochemical fibre types were affected but the changes were more pronounced in type 1 than in type 2 fibres (Fig 8 a 8 b)

Electron microscopy of deltoid muscle The alterations were similar to those described in the rectus superior muscle The degenerative changes found in the muscle fibres were conspicuous with large aggregations of giant mitochondria located under the sarcoplasma membrane and between the fibrils These organelles were often bizarre with an abnormal configuration and a varied arrangement of the cristae inside the mitochondria Several mitochondria contained multiple crystalline inclusions within the cristae especially the giant elongated ones Vacuoles glycogen granular and osmiophilic material were also seen These were often present in the same mito chondrion together with the crystalline inclusions Lipid and osmiophilic bodies often lay close to the mitochondria Mitochondria containing a granular material and/or vacuoles were observed in a capillary vessel wall (Figs 9 a 9 b 10 a 10 b)



Fig 10 a and b
Left deltoid muscle Closely packed mitochondria (Mi) showing d uble and tr ple membranes Certain of the mitochondria conta n electron dense granules wh le others appear empty Note also the club shaped mitochondria w th rystalline nclusions × 7, 000 (Case 4 EM 75f)

Discussion

The material comprised four patients who had a chronic progressive external ophthalmoplegia with a variety of additional findings which are summarized in Table I In all of the patients abnormalities of muscle fibres were seen Light microscopy showed the characteristic red colour of muscle fibres with Gomori s trichrome stain Electron microscopy revealed pronounced mitochondrial alterations A characteristic feature in these patients was a marked proliferation of mitochondria which were much larger than normal and often quite bizarre The internal structure of the cristae was complex with elongated crystalline inclusions Abnormalities of muscle fibres were found including "contraction clumps which have also been described in families with malignant hyperthermia (Reske Nielsen et al 1975) The levator palpebrae muscle of case 4 showed an almost complete replacement of muscle fibres by connective tissue and fat cells with a marked loss of nerve fibres and myelin sheaths Two end plates were observed the secondary synaptic clefts were displaced by closely packed abnormal mitochondria These findings were compared with normal muscle tissue obtained from healthy young individuals (Reske Nielsen & Harmsen 1972) Similar findings in ophthalmoplegia have been described by several authors (von Wijngaarden et al 1967 Pateisky et al 1970 Morgan Hughes & Mair 1973 Karpati et al 1973 Schneck et al 1973 Shapira et al 1975 Schlote & Korner 1976)

In the present study the abnormal mitochondria were not only found in muscle tissue but also to a much lesser extent in fibrous tissue and endothelial cells of blood vessels The fact that other tissues are involved is in agreement with other authors In patients with opthalmoplegia Gonates (1967) found abnormal mitochondria in liver cells Karpati et al (1973) found them in sweat glands and Schneck et al (1973) found them in cerebellum This indicates that the morphological mitochondrial abnormality is universal

The cases reported in the literature and in the present study comprise a complicated collection of symptoms and signs derived from different organs which cannot immediatedly by explained in any one particular way The main organs involved are the extraocular muscles the myocardium the retina (probably the pigment epithelium) the central nervous system and the endocrine organs These structures characteristically have large metabolic requirments which are mainly provided by carbohydrate metabolism (Altman & Dittmer 1971)

The morphological findings are considered compatible with a metabolic defect located in the mitochondria In order to attempt to explain the above mentioned mitochondrial changes the problem was examined from a biochemical

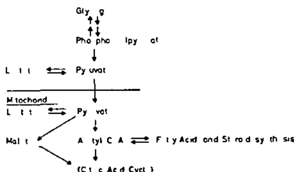


Fig 11
A schematical representation of the biochemical pathway involving pyruvate and lactate metabolism

point of view Pyruvate metabolism was studied and the blood levels of pyruvate and lactate were measured Increased levels of these metabolites were found in the three patients who had the most pronounced ultrastructural alterations in the biopsies In three patients (1 3 and 4) an increase in lactate and in two patients (1 and 4) an increase in pyruvate were demonstrated The findings suggest a defect in pyruvate metabolism (Fig 11) Increased blood levels of pyruvate and lactate have not previously been demonstrated in ophthalmo plegia plus

The mitochondrial changes could be explained by the defect in the pyruvate lactate metabolism with a block in the metabolism of pyruvate and decreased activity of the citric acid cycle The enzyme systems involved are located in the mitochondrial cristae In our opinion the proposed biochemical defect could be the primary factor responsible for the extreme proliferation of the abnormal mitochondria

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MAY TRICHOMONAS VAGINALIS PROVOKE CONJUNCTIVITIS?

BY

M S NORN F LUNDVALL and P PÆRREGAARD

In the world literature we have found descriptions of five cases of Trichomonas vaginalis in the conjunctiva
Conjunctival swabs taken from 1?2 patients with conjunctivitis or keratitis revealed no flagellate micro organisms on phase contrast microscopy and culture Neither did conjunctival swabs from 27? newborn infants in spite of the fact that 5 / per cent of their mothers had Trichomonas in the vagina Trichomonas vaginalis is hardly likely to be responsible for conjunctivitis

Key words conjunctivitis – oculogenital diseases – Trichomonas vaginalis

Oculogenital disease in a restricted sense is an eye disease known to be produced or probably produced by ocular contamination with genital discharges from local genital disease (Thygeson 1971)

Gonorrhoeal ophthalmia neonatorum and Chlamydia infection (inclusion conjunctivitis of the newborn swimming pool conjunctivitis lymphogranuloma venereum) are typical examples Other examples are herpes genitalis (type ? herpes) fungi phthirus pubis (morpion louse) and perhaps lactobacillus sp Doderlein

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Increasing promiscuity altered sexual practice and homosexuality have contributed towards an additional interest in the oculogenital diseases

Trichomonas vaginalis (trix = hair monas = unit) is a protozoon (unicellular organism) having 3–5 flagella It lives in the acid vaginal environment (pH 4 5–6 0) and may be transferred by contamination to the male urethra and possibly to bladder and prostate It is present in about 25 per cent of all women suffering from a venereal disease (Ruth Nielsen 1973)

In 1961 Robinson detected Trichomonas vaginalis in 47 8 per cent of a series of pregnant women Seven days after the delivery he found the incidence was 39 5 per cent

In 1965 Robinson found an incidence of 31 per cent in a similar series

Notelovitz in 1974 disclosed Trichomonas vaginalis in 11 2 per cent of a group of pregnant women with no signs or symptoms of vaginitis and in 17 5 per cent of pregnant women with signs of vaginitis

Disagreement prevails as to whether the incidence of Trichomonas vaginalis is higher (Magnin 1966) or lower (Bredland 1962) in pregnant women than in non pregnant women of the same age class

Trichomonas vaginalis may possibly provoke oculogenital disease Thygeson (1971) has never seen any such cases but mentions a case reported by J L McGraw of Syracuse USA (personal communication)

Siedlecka & Seveced (1971) have described four Polish cases of conjunctivitis induced by Trichomonas vaginalis Three cases occurred in health service workers engaged in treatment or examination of patients with Trichomonas vaginalis and one patient was a girl aged three years whose mother had vaginal trichomoniasis All four cases were allegedly cured by treatment with metronidazole

Numerous attempts have been made to *inoculate experimental animals* with Trichomonas vaginalis for the purpose of obtaining a reliable model for testing anti Trichomonas drugs

Culture in animals is difficult. In the vagina this has only been possible in rhesus monkey and common hamster In mice culture has been carried through intraperitoneally intramuscularly and subcutaneously In rabbits Trichomonas can be cultured in the anterior chamber of the eye especially if the injection has caused damage to the lens that is abnormal aqueous humour (Weld & Kean 1956 1958 Gualdi & Fabio 1959) Culture failed in conjunctival and corneal tissue of rabbit and guinea pig (Gualdi & Fabio 1959)

Presence of the flagellate micro organism Trichomonas vaginalis is best shown by culture and direct by phase contrast microscopy Ordinary microscopy

played an important role in the newborn infant s eye we should expect the parasite to multiplicate at this point of time

Other flagellate micro organisms are demonstrable in other human regions Trichomonas intestinalis in coecum and colon and a different one in the oral cavity The result of the present investigation based on inoculation of swabs from 394 conjunctivas suggests that flagellate organisms cannot thrive in the conjunctiva At any rate they are extremely rare in this region

The conclusion must therefore be drawn that Trichomonas vaginalis is unlikely to play any pathogenic role in the eye region

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RETINAL FUNCTIONS IN DOMINANT CYSTOID MACULAR DYSTROPHY (DCMD)

BY

A PINCKERS A F DEUTMAN and J G A NOTTING

Dominant cystoid macular dystrophy (DCMD) occurred in 28 members of 5 unrelated families The disease is characterized by cystoid macular oedema and leakage from retinal capillaries in the posterior pole Colour vision examination reveals a type I red green defect with concomitant blue yellow defectiveness the latter may be caused by the leaking capilla ries The ERG is normal The EOG is subnormal Darkadaptation curves are often slightly disturbed There are frequently also aspecific pigmentary alterations in the peripheral fundus

Key words DCMD – dominant macular dystrophy – colour vision – ERG – EOG – DA curve

Dominant cystoid macular dystrophy (DCMD) is characterized by cystoid macular oedema macular pigmentary changes mild punctate vitreous opacities and hyperopia with fine folding of the inner limiting membrane (Deutman Pinckers & Aandekerk 1976 Notting & Pinckers 1976) The macular pigment changes may sometimes resemble a bull s eye picture in some cases an atrophic macular lesion develops at a later stage

We found DCMD in five unrelated families and we describe here the results of functional examination

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Material and Methods

In five families 28 subjects presenting with DCMD were examined by means of colour vision tests in some cases EOG ERG and darkadaptation curves were performed A follow up was carried out in 9 cases in some of them of up to a period of 4 years

Colour vision examination included the AO H R R test Ishihara XIIth ed F2 plate Panel D 15 (some cases retested with Lanthony s desaturated Panel) FM 100 Hue and Nagel anomaloscope model II Codification of test results was according to François & Verriest (1957) The illumination of 1750 Lux was by means of 6 Philips fluorescent tubes colour 57 placed 1 m above the examination table

The ERG and EOG method was the same as that described by Thijssen Pinckers & Otto (1974) The darkadaptation curve was obtained according to the method of Goldmann Weekers The family history strongly suggested that individuals listed as probably affected had also DCMD (age of onset inability to finish studies because of poor visual acuity the family members examined know that the disease is common in their family)

Results

The results are summarized in Tables I and II

Table II

Results of examination with the F2 plate AO H R R and Ishihara XIIth ed

Tritan plate (49 eyes) Codification				AO H R R (49 eyes)		Ishihara XIIth ed (44 eyes) Codification				
G–B–	G+B–	G = B	G > B	No	codification	P < D	P = D	CE+	Cpa	S+ rest I
0	6	2	23	31	normal	18	7	0	[illegible]	0
1	2	0	4	7	mild RG	4	4	0	6	1
0	1	0	0	1	medium RG	1	0	0	1	1
3	5	0	1	9	RG + BY	1	8	0	4	8
0	1	0	0	1	BY	1	1	0	0	0

Electroretinography (ERG) was performed in 20 subjects 18 displayed a normal ERG In 2 cases the ERG was diminished

Subject D III-4 had a L E diminished cone function for an unknown period he had an elevated IOP (more than 50 mmHg) on his first visit his L E visual acuity was reduced to 0

Subject E III 2 had a diminished cone and rod function in both eyes the fundi showed not only DCMD but also pigmentary degeneration in both superior temporal quadrants

Electro oculography (EOG) was performed in 25 patients (48 eyes) the Lp/Dt ratio was 1 85 or more in 17 eyes 1 50 or less in 24 eyes and between 1 50 and 1 85 in 7 eyes At follow up examination the Lp/Dt ratio tended to fall (case A II 5 A II 7 A III 4)

Darkadaptation curves were carried out in 7 subjects in the 2 cases with normal darkadaptation depth the EOG was also normal Of the 5 cases with disturbed darkadaptation only 1 case (no II 5) had a normal EOG

Colour vision examination revealed an acquired type I red green defectiveness only one subject (E IV 12) showed a blue yellow defect

Anomaloscope The acquired type I defect becomes manifest with anomaloscope examination initially the equation zone broadens towards the red later on also Rayleigh s match is displaced towards the red In early cases the AO H R R results may be still normal but the Ishihara readings are not In advanced stages the anomaloscope equation zone broadens also to the green but we never saw an achromatic stage similar to that found in cone dystrophy

AO H R R Once the AO H R R results have to be classified as medium red green defectiveness there is a concomittant blue yellow defect (Table II)

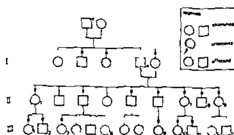


Fig 1
Pedigree of family A

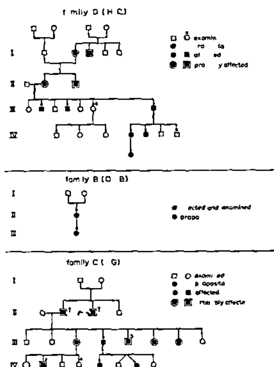


Fig 2
Pedigrees of the families B C and D

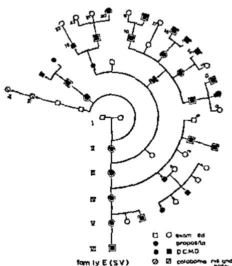


Fig 3
Pedigree of family E

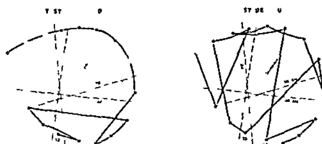


Fig 4
Panel D 15 retest desaturated Panel R E subject B III 1

Ishihara XIIth ed The Ishihara was normal in only 2 cases There was never a CE+ reading pa readings indicating red green confusion were observed to a moderate degree in about 40 % The plates designed to differentiate be tween protan and deutan defects were never read as protan indicative ($P > D$ in about 55 % more deutan symbols ($P < D$) were correctly interpreted Once the AO H R R is classified as medium red green defect only the S plate is seen the other symbols are missed (Table II)

Tritan (F2) plate The greater the acquired colour vision defect the more the F2 plate readings are incorrect there is however no direct relationship between AO H R R and F2 plate results

Desaturated Panel D 15 Only a few cases were examined with the desaturated Panel D 15 the test results may reveal red green confusions when the AO H R R still indicates normal colour vision

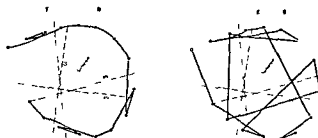


Fig 5
Panel D 15 retest desaturated Panel L. E subject B III 1

Subject B III-1

R E AO H R R normal Panel D 15 1//DT 1//T+ 1ME retest desaturated D 15 x2//P 1//D 2//DT (Fig 4)

L E AO H R R normal Panel D 15 3ME retest desaturated D 15 x2//P 1//PD 1//DT 2//T 1//T+ (Fig 5)

While the desaturated D 15 shows fault positive blue yellow confusions (Pinckers Nabbe & v d Bogaard 1976) as does the original Panel D 15 the red green confusions are significant being neither detected by the AO H R R nor by the Panel D 15

FM 100 Hue An elevated total FM 100 Hue error score (CI) is an early finding sometimes there is no clear confusion direction in most cases however the FM 100 Hue pattern shows a red green error accumulation with a con comitant blue yellow error accumulation

Discussion

DCMD appears at an early age probably earlier than Stargardt s disease or dominant progressive foveal dystrophy DCMD is characterized by

Hyperopia fine folding of the inner limiting membrane and decreased visual acuity

Foveal pigment dispersion in some cases slowly progressing to a bull s eye

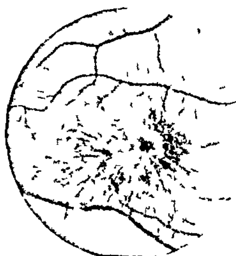


Fig 6
Foveal pigment dispersion



Fig 7
Slight peripheral pigmentary disturbance

pattern at later stages there is a tendency towards increasing macular atrophy in the meantime the peripheral fundus shows some slight pigmentary disturbance (Figs 6 and 7)

Cystoid macular edema with leakage from the capillaries in the posterior pole (Fig 8)

A variable degree of punctate and strand like vitreous opacities

An acquired type I red green defectiveness starting as a slight disturbance without predominant confusions the diminished anomaloscopic red sensitivity is the first sign once a medium red green defect (AO H R R) is established a concomitant blue yellow defectiveness becomes evident

Normal ERG findings whereas the EOG and the darkadaptation curves are often subnormal

Autosomal dominant inheritance in our material the family members affected by DCMD are equally distributed among both sexes In the pedigrees A C D and E DCMD is transmitted from father to son father to daughter mother to daughter and mother to son

A relatively unfavourable prognosis as far as visual acuity is concerned from Table I it is evident that visual acuity may fall to less than 0 1

DCMD must be differentiated from other dominantly inherited macular dystrophies with an acquired type I red green defectiveness In the dominantly inherited form of *progressive cone dystrophy* described by Deutman (1971) and by Pearlman Owen & Brownley (1974) there is an evident ERG cone

dysfunction while in DCMD the ERG is normal *Central cone involvement only* (Krill Deutman & Fishman 1973) presents a type I colour vision defect but a normal ERG there is some evidence that after some years the ERG reveals a definite cone abnormality and in such cases central cone involvement must be regarded as an early stage of progressive cone dystrophy In DCMD we did not find ERG cone impairment While in central cone involvement there is a typical acquired type I red green defect the type I defect in DCMD becomes complicated by an acquired blue yellow defect

In the past cases of DCMD have been tentatively classified as a dominantly

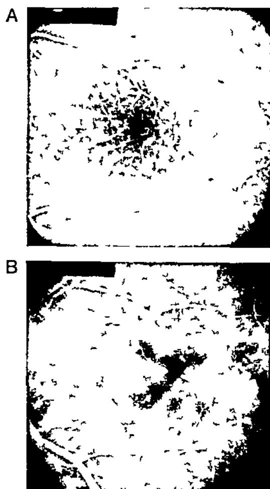


Fig 8

Fluorographic study with dilated retinal capillaries in the arteriovenous phase (A) and the picture of cystoid macular oedema in the late phase (B)

inherited juvenile macular degeneration Extending our examination with fluo rescein angiography (19 cases) colour vision ERG and EOG we were able to distinguish DCMD as a separate clinical entity Stargardt is considered as an autosomal recessively inherited disease in virtually all cases flavimaculatus flecks are seen but there is no cystoid edema and no early blue yellow defi ciency Some publications dealing with dominant foveal dystrophy or domi nant Stargardt may possibly include cases of DCMD

François (1963) observed macular microcysts in juvenile macular degenera tion but this was probably a case of sex linked juvenile retinoschisis In sex linked juvenile retinoschisis the most frequently observed colour vision defect is a blue yellow type but according to Pinckers Nabbe & v d Bogaard (1976) a type I red green defect is not excluded The ERG changes in sex linked juvenile retinoschisis concern primarily the *b* wave (Deutman 1971)

It is intriguing that in DCMD there are changes at different levels in the retina Chronic cystoid oedema caused by increased permeability of the retinal capillaries may give rise to an acquired blue yellow defect Secondary pigmen dispersion on the basis of chronic cystoid oedema can also explain the occur rence of blue yellow defect There is however evidence that the pigment epi thelial layer is primarily involved The disturbed EOG and darkadaptation curves point to lesion in the peripheral pigment epithelial rod complex this process seems to be very slow since it does not result in an overall diminished rod function (ERG) If there is a primary lesion of the pigment epithelium in the macular area as well this could be a third explanation of the B Y defect

It is generally accepted that an acquired type I red green defect is a symptom of circumfoveolar cone damage A type I defect is predominant in DCMD although it never progresses to an acquired central achromatopsia Neither the cystoid oedema nor the pigment alterations can sufficiently explain the occur rence of the type I defect

Conclusion

DCMD is a distinct clinical entity Papers concerning dominant progressive foveal dystrophy or so called dominant Stargardt s disease may include cases of DCMD The ERG is normal The EOG is often disturbed The darkadapta tion curve also is often disturbed There is a type I acquired colour vision defect which does not result in an acquired (central) achromatopsia at a relatively early stage there is a concomitant blue yellow defect Increased permeability of the retinal capillaries as well as involvement of the pigment epithelial layer seem to be responsible for the clinical findings

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ETIDOCAINE IN RETROBULBAR ANAESTHESIA

A Comparison with Mepivacaine

BY

W THORBURN A M THORN ALQUIST and H EDSTRÖM

A new long acting local anaesthetic etidocaine (Duranest®) has been compared to mepivacaine (Carbocaine®) in retrobulbar anaesthesia in a double blind trial including 45 patients Solutions used were etidocaine 0 5 % and 1 % and mepivacaine 1 % all without adrenaline The onset time was short and no difference was found between the solutions The duration of analgesia and motor block was significantly longer with etidocaine 1 % compared to mepivacaine 1 % In a following open study with etidocaine 1 % and mepivacaine 1 % about 80 % of the the patients in the etidocaine group never experienced any post operative pain compared to about 50 % in the mepivacaine group No signs of local or systemic toxicity were noted in the studies

Key words etidocaine – intraocular surgery – mepivacaine – retrobulbar anaesthesia

Presented in part at the 1 th Congress of the Scandinavian Society of Anaesthesiologists July 7–12 19 5 and at the Meeting of the Swedish Ophthalmological Society November 28 1975

Etidocaine (Duranest®) is a new local anaesthetic of relatively low toxicity which provides a block of long duration with good sensory and motor blockade (Engberg et al 1974) In order to evaluate its usefulness in eye surgery etidocaine 0 5 % and 1 % were compared with mepivacaine 1 % all solutions without adrenaline in retrobulbar anaesthesia

Materials

The double blind study (A) included 45 cooperative inpatients who required retrobulbar anaesthesia prior to ocular operations The patients were premedicated with pethidin and prometazin (Lergigan®) one h before the operation with dosages according to age For further details concerning mean operation time etc see Table I A similar open study comprised of 100 patients was carried out study B (see Table II)

Study A

The anaesthetic solutions used were mepivacaine 1 % etidocaine 1 % and etidocaine 0 5 % all without adrenaline

Study B

The anaesthetic solutions used were etidocaine 1 % and mepivacaine 1 % both without adrenaline

Table I
Patient distribution on the basis of age and disease study A

	Mepivacaine 1 %	Etidocaine 0 5 %	Etidocaine 1 %
No of patients	1	14	16
Age mean (range)	71	2	70
	(31–85)	(53–84)	(25–84)
Disease			
cataract	10	9	11
glaucoma	5	4	4
retinal detachment	0	1	1
Mean op time (min)	47	49	50

Table II
Patient distribution on the basis of age and disease study B

	Mepivacaine 1 %	Etidocaine 1 %
No of patients	50	50
Age mean (range)	72 (19–89)	71 (31–93)
Disease		
cataract	36	28
glaucoma	14	22

Methods

Retrobulbar anaesthesias were performed by the same surgeon as follows First a retrobulbar injection was made through the lower eyelid at the lateral margo orbitalis A quantity of 2 ml of the local anaesthetic agent was injected into the muscle cone Secondly another injection was made through the upper eyelid and 1–1 5 ml given around the upper rectus muscle To achieve lid block a modified van Lindt technique according to Atkinson was used and the total volume injected was 5 ml

Study A

The onset of analgesia was evaluated by pin prick in the medial and the lateral parts of the conjunctiva about 5 mm from the cornea every two min for 8 min after the completion of the injections At the same time akinesia was estimated by asking the patient to move the eye in the four main directions

Immobility was noted even if some residual function of the extraocular muscles was present Analgesia and akinesia was also tested immediately after the operation and the patient was questioned about ocular pain

The duration of analgesia was followed by asking the patients about subjective postoperative pain once every hour after injection for six h The duration of akinesia was tested at the same time

Study B

Here only the postoperative analgesia was studied by asking the patients postoperatively to report all sensations of pain as soon as they occurred during the next 24 h

Results

Study A

Onset time The onset of analgesia (Fig 1) and akinesia (Fig 2) was generally rapid No difference was found between the different solutions (Kolmogorov Smirnov s test) Fig 1 shows the results of the medial conjunctiva a similar result was obtained in the lateral conjunctiva where however only 70 % of the patients (in all groups) experienced complete analgesia The reason for this is the common occurrence of small sensory branches to the temporal con junctiva from the lacrimal nerve which are little affected by the retrobulbar injection In six patients equally divided among the groups the primary analgetic effect at the temporal conjunctiva was not sufficient and 0 1 ml of the same anaesthetic solution used in the initial injection had to be given subconjunctivally for complete analgesia

Analgesia at the end of the operation The results are given in Fig 3 No dif ference was found between the anaesthetic solutions (χ test)

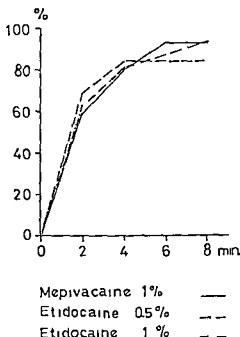


Fig 1
Onset of analgesia of medial conjunctiva shown as cumulative percentages of eyes at different time intervals

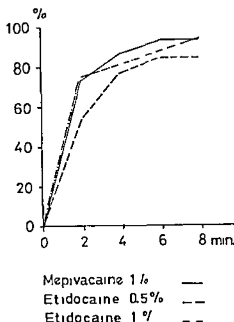


Fig. 2

Onset of akinesia shown as cumulative percentages of eyes at different time intervals

Duration of analgesia. The proportion of patients with postoperative pain at each time interval is shown in Fig. 4. Six h after injection the percentage of patients without pain was in the mepivacaine group 14, in the etidocaine 0.5% group 39 and in the etidocaine 1% group 63. The difference between mepivacaine 1% and etidocaine 1% was significant (χ^2 test, $P < 0.05$).

Duration of akinesia. The proportion of patients with normal motility of the eye within the first six h after injection are given in Fig. 5. The difference between mepivacaine and etidocaine, both concentrations, was significant ($P < 0.05$ and $P < 0.001$, Kolmogorov-Smirnov's test). No difference between etidocaine 0.5% and 1% was found (Kolmogorov-Smirnov's test). After six h all the patients in the mepivacaine group had normal motility, the corresponding values in the etidocaine groups were 54% and 20%. In all cases, however, normal motility was restored after about 24 h.

Study B

The results are given in Tables III and IV and Fig. 6. In the mepivacaine group 54% of all patients reported postoperative pain. The mean duration of

Results

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Analgesia at the end of the operation The results are given in Fig 3 No difference was found between the anaesthetic solutions (χ test)

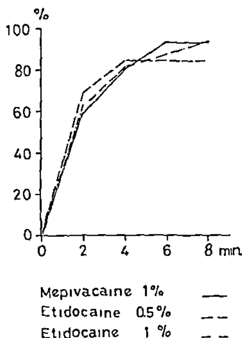


Fig 1

Onset of analgesia of medial conjunctiva shown as cumulative percentages of eyes at different time intervals

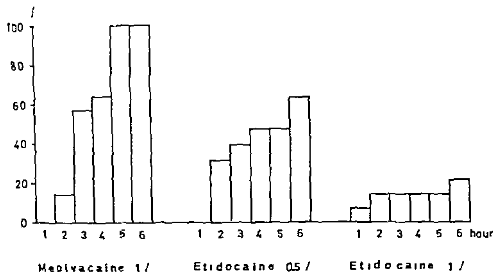


Fig 5

Proportion of patients with normal motility of eye at different time intervals after retrobulbar anaesthesia

analgesia in those reporting pain was about five and a half h In the etidocaine group 22 % the patients reported pain the corresponding mean time here was about seven h

No complications or toxic reactions were observed during the study and burning sensation was absent during injection Satisfactory anaesthesia was achieved in all operations No difference in bleeding tendency was observed

Table III

Percentage of patients with post operative pain study B

Disease	Mepivacaine	Etidocaine
Cataract	3 %	[illegible]5 %
Glaucoma	7 %	18 %
Total	4	22 %

Table IV
Patients with pain Mean time interval between injection and pain study B

	Mepivacaine	Etidocaine
Mean interval	332 min	425 min

Discussion

In intraocular surgery there is a need not only of good analgesia during the operation but also of good relaxation of the orbicular and extraocular muscles A long acting anaesthetic agent would reduce the postoperative pain that makes patients restless and worried and thus reduce the need for analgetics It is also advantageous with a profound motor block of long duration to avoid squeezing of the lids and movements of the eye during the initial postoperative period

One way of increasing the duration of the anaesthetic effect is to add adrenaline to the local anaesthetic agent This method is advocated by some ophthalmologists The ability of adrenaline to prolong the duration of an

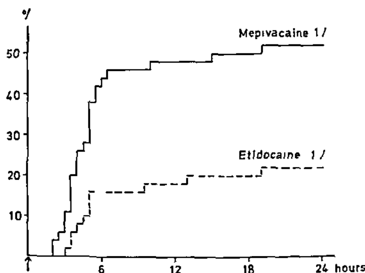


Fig 6
Cumulative percentage of patients reporting pain at different time intervals after injection (arrow)

aesthesia is partly dependent of the kind of anaesthetic and partly of the site of injection For example adrenaline markedly prolongs the duration of action of lidocaine (Lofstrom 1970b) an effect not seen at least not to the same degree with mepivacaine (Albert & Lofstrom 1965) The duration of action of bupivacaine was not increased by the addition of adrenaline (Löfström et al 1970a Moore et al 1970 Laaka et al 1972) The effect of site of administration is studied by e g Dhuner & Lewis (1966) who studied regional blood flow after injections of mepivacaine lidocaine and bupivacaine with and without the addition of adrenaline They found different effects on blood flow when the anaesthetic agent was injected in different locations No information is available about the ocular blood flow in connection with retrobulbar anaesthesia

There seems to be some danger of damage to the optic disc by using adrenaline in retrobulbar anaesthesia for glaucoma surgery A constriction of the small arteries supplying the posterior pole of the eye might cause ischaemia of the optic disc Another reason not to give adrenaline is that many patients especially elderly ones have cardiac diseases With this in mind the present study was performed without adrenaline

The onset of anaesthesia of mepivacaine 1 % was rapid which is in agreement with other studies of this agent (Castren 1963 Laaka et al 1972) The onset of anaesthesia after etidocaine 0.5 % and 1 % was comparable to that of mepivacaine (Figs 1 and 2)

The duration of action was shorter for mepivacaine 1 % compared to etidocaine 1 % with regards to both analgesia and akinesia In the mepivacaine group both analgesia and muscle relaxation subsided at about the same time In the etidocaine groups the duration of the motorblock appeared to be longer than that of analgesia This has been a matter of discussion In ulnar nerve blocks Lofstrom (1975) noted longer duration of muscle block than of analgesia contrary to the results of Radtke et al (1975) This is however of secondary importance in this type of surgery but it is an advantage for the outcome of the operation that akinesia persists during the first hours after operation

In study A the mean duration of postoperative analgesia among patients in the mepivacaine group who got postoperative pain was about 200 min (Fig 4) while in study B it was 330 min (Table IV Fig 6) The difference is due to the long follow up in study B Despite the difficulty of comparison caused by the methods used by different authors it is of interest to compare the present results with the durations reported for some other anaesthetics Mepivacaine 2 % with adrenaline 195–292 min (Castren 1963) 217 min (Laaka et al 1972) Lidocaine 2 % with adrenaline 190 min (Castren 1963) Bupivacaine 0 5 % with adrenaline 350 min (Castrén & Tammisto 1966) respectively 300 min

(Laaka et al 1972) and without adrenaline 300 min (Laaka et al 1972) With etidocaine 1 % without adrenaline we reached 420 min for mean postoperative analgesia (Table IV) However the greatest asset of etidocaine is that only a few (22 %) of the patients ever experienced pain

It is quite clear from this study that etidocaine in a concentration of 1 % gives sufficient analgesia for intraocular surgery and also reduces the percentage of patients with postoperative pain Furthermore there seems to be no need for adrenaline addition In conclusion etidocaine is a valuable drug in ophthalmic surgery with low toxicity rapid onset and long duration of action

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CONGO RED VITAL STAINING OF CORNEA AND CONJUNCTIVA

BY

M S NORN

Vital staining with an aqueous solution of 1 % Congo red has been studied in the slit lamp In 98 cases the dye was mixed with 1 % lissamine green in 120 eyes subsequent staining was performed with 0 1²5 % fluorescein and in 80 cases the mucous thread from the inferior conjunctival fornix was microscoped

Congo red stains dead cells degenerate cells and mucus The dye discloses keratitis corneal erosion contact lens damages corrosions etc It stains like lissamine green and rose bengal though less frequently and less intensely than these

Congo red is a pH indicator Acid reaction beyond its pH range (3 0–5 2) has not been demonstrated

Amyloid specific colour reaction (red green dichromatic polarisation) has been noticed in mucous fibrils most often in relation to infectious conjunctivitis and corrosion, never in normal eyes Th phenomenon is believed to indicate degeneration of the mucous fibrils (on the analogy of toluidine blue stained mucus) whereas not presence of genuine amyloid It is in other words an important phenomenon in the differential diagnosis

Congo red is hardly indicated in ordinary clinical practice for vital staining of cornea and conjunctiva Fluorescein combined with rose bengal or lissamin green should be preferred

Key words vital staining – polarisation – Congo red – amyloid – acidity – cornea – conjunctiva

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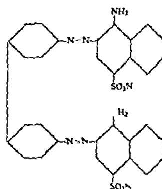


Fig 1
Congo red

Congo red (Congazonnatrium Nord 63 dianil red direct red Y microme no 400 Kongorot formula Fig 1) was first synthesized by Bottiger in 1884 or two years later than rose bengal

Congo red is an acid diazo dye soluble 1–25 in water almost insoluble in ether xylol and chloroform The compound is used for direct dyeing (i e without a mordant) of cellulose containing fabrics (Gurr 1960 Tooley 1971)

Within biology it was used as early as 1886 by Scholz for staining *Rotatoria* (wheel animals) and later for staining cellulose in plant sections bacterial walls and histological preparations

A factor of particular interest is the detection of amyloid Congo red is the most specific dye for demonstrating these abnormal protein deposits A dichromatic polarisation (red and green) is specific to amyloid Within the eye region such deposits have been noticed in the vitreous body (*e g* by Hitchings et al 1976) in the orbit (Gromowski et al 1965) subconjunctivally (e g by Norn 1964) and in the cornea perhaps even in the epithelial tonofibrils (Garner 1969)

Congo red can be injected intravenously as a test for presence of amyloid in the organism

Congo red is a pH indicator blue in acid solution and red in neutral and alkaline with a pH range of 3 0–5 2 The light absorption of the red colour is maximum at 495 ± 1 mμ

Congo red has not been used before as a vital stain for the external eye

The objects of the present study have been to assess the vital staining properties of Congo red when in contact with cornea and conjunctiva further to rank the dye in the system of known vital stains (Norn 1974) and to investigate whether it has special properties of practical value as a vital stain

Present Investigations

Congo red can be used in a 1 % aqueous solution It then does not precipitate and accordingly gives no false vital staining

The solution causes no smarting pain when instilled into the eye (unlike rose bengal) It stains the mucous thread in the inferior conjunctival fornix and pathological structures on the cornea Congo red does not effect tattooing (as do alcian blue and tetrazolium)

The Congo red stained areas of the cornea and the conjunctiva show punctate staining always red never blue Instillation into the conjunctiva of a buffer of pH 4 5 (acetic acid and sodium acetate) leaves the colour practically unaltered On the other hand the same buffer poured over a vital stained red mucous thread transferred to a slide effects intense blue colouring of the thread in some places

Slit lamp

The vital staining properties of Congo red were studied partly *in vivo* in the slit lamp after admixture of lissamine green and fluorescein respectively and partly by microscopy of the vital stained mucous thread

Method and Material

Comparison with lissamine green was performed by using a mixture of 1 % Congo red and 1 % lissamine green The mixture did not precipitate The two dyes preserved their specific properties Thus some structures were stained green by lissamine green some only red by Congo red and some blue by both components By using a dye mixture we obtained simultaneous introduction of both dyes in correct proportions

One drop (10 μl) was instilled into the conjunctival sac through a cannula mounted on a dropping bottle After few minutes excess dye had been removed by the tears and the result could be read in the white light of the slit lamp

The colour intensity in the different regions was read graded in the arbitrary grades 1 to 5 Grade 3 represents medium staining 2 weak staining 4 intense 1 minimum and 5 maximum The grading of each colour (green blue red) was noted in a diagram for each patient

A total of 98 eyes were examined with main concentration on corneal lesions (Table 1)

Table I
Clinical diagnoses for eyes examined in the slit lamp

	Lissamine green + Congo red	Congo red + fluorescein
Normal	15	23
Keratitis	20	29
Corneal erosion	10	9
Corrosion foreign body	5	11
Graft	3	2
Sicca dry eye	11	3
Infectious conj	3	14
Allergic conj	2	3
Chron simple conj	1	8
Episcleritis	2	3
Exophthalmos	2	1
Contact lens	14	3
Other	4	5
Total	98	120

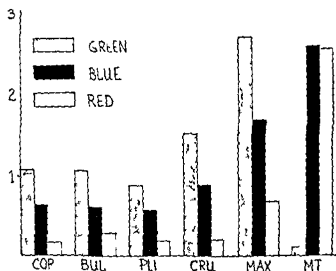


Fig 2
Vital staining profile for a mixture of lissamine green and Congo red Mean staining grades in the following regions cornea bulbar conjunctiva plica semilunaris caruncle Marx line and mucous thread in inferior conjunctival fornix A total of 98 eyes

In another series staining was performed first with 10 μl of 1 % Congo red and then with 10 μl of 0 125 % fluorescein The colour due to Congo red was read in the white light of the slit lamp and that due to fluorescein in cobalt filtered light

The series comprised 120 eyes The diagnoses are shown in Table I

Results

Mixture of Congo red and lissamine green

Fig 2 illustrates the mean staining grade in the individual regions The mean staining grades for the cornea were 1 06 by lissamine green alone 0 62 by both dyes combined and only 0 16 by Congo red alone

Table II shows that the cornea was stained by lissamine green in 48 per cent of the cases by both dyes in 38 per cent and by Congo red alone in no more than 14 per cent

Fig 2 illustrates the profile for all regions The staining grade proportions are seen to be approximately the same within the different regions (cornea bulbar conjunctiva plica semilunaris caruncle and Marx line) The mean staining grade is seen to have been the highest for lissamine green and somewhat lower for both dyes combined while Congo red rarely stained alone The inferior fornix and the palpebral conjunctiva were hardly ever stained

Table II shows that the regions were most often stained by lissamine green more rarely by both dyes combined and extremely rarely by Congo red

However the mucous thread in the inferior fornix differed definitely from the other regions It was stained as often (Table II) and as intensely (Fig 2)

Table II

Incidence (in per cent) of vital staining in the various regions (cornea bulbar conjunctiva, plica semilunaris caruncle Marx line and mucous thread) using Congo red followed by fluorescein or a mixture of lissamine green and Congo red

		Cornea	Bulb	Plica	Caruncle	Marx	M T
Congo red	red	35	20	15	42	86	96
fluorescein	yellow	31	3	1	12	0	0
Mixture of	red	14	17	9	12	53	95
Congo red and	blue	38	32	31	57	84	94
lissamine green	green	48	49	45	71	92	5

Table III

Mucous thread vital stained by Congo red Size of mucous thread area and of polarized regions measured by means of a measuring ocular in different clinical states

	Non polarized red	Polarized			No of eyes
		red	green	white	
Normal	9 2±2 2	0 003±0 003	0	0 5±0 2	11
Keratitis	10 2±2 2	0 10±0 06	0 001±0 009	0 3±0 2	10
Corrosion	7 6+1 6	1 2±0 5	0 05±0 04	0 005±0 22	9
Infectious conj	12 2±2 2	1 1±0 6	0 3±0 3	0 6±0 2	10
Simple chron conj	5 2±1 5	0 8±0 [illegible]	0	0 6±0 6	8
Episcleritis	2 8	0 3	0 03	0 1	1
Other*	13 2±4 4	0 07±0 06	0 0004±0 0003	0 2±0 1	10

* Other comprise keratoconjunctivitis sicca (3) allergy (3) and one case each of meibomitis contact lens graft reaction and glycerol instillation

Congo red alone

In mucous threads from 52 eyes vital stained by Congo red the dye was found to have stained mucous fibrils and a number of cells (neutrophilic and eosinophilic granulocytes epithelial cells) while other cells remained unstained

Table III shows the sizes of the areas stained in different clinical states The results are in fair agreement with those of previous studies after staining with a mixture of alcian blue and tetrazolium (Norn 1972)

Examination with crossed polarizing filters revealed mainly white polarisation less frequently red and most rarely green

White polarisation was due to foreign bodies in vacuoles of the mucous thread (cf Norn 1969) or white polarizing mucous fibrils

Red polarizing fibrils were detected in 71 per cent of 52 eyes Such fibrils were especially present in cases of bacterial infectious conjunctivitis and corrosion whereas they were noticed in very small numbers only in normal eyes

Green polarizing fibrils were scarce and if present always in mucous threads with red polarizing fibrils as well This phenomenon may be characterized as Congo red dichroism and is specific of amyloid It was detected in 23 % of the eyes

In the presence of dichroism we saw green polarizing fibrils running at right angles to red polarizing fibrils or being continuous with red polarizing The fibrils seemed to continue their course as red non polarizing fibrils

Discussion

The present investigation gave the result that 1% Congo red is useful as a vital stain for examination of cornea and conjunctiva Congo red has approximately the same properties as lissamine green but the staining is much weaker than that by lissamine green

Lissamine green was chosen for comparison with Congo red because it is suitable as a contrast stain in mixture with Congo red and its staining properties are practically identical with those of the well known rose bengal (Norn 1974)

Sauter (1976) has studied xerophthalmia (vitamin A deficiency) one of the most frequent causes of blindness He found rose bengal or lissamine green to be the most reliable vital stains for disclosing the disease at its initial stage Further he found their staining properties to be equal Nevertheless he preferred lissamine green because it causes no smarting pain and because the green colour is easier to see at a distance

The present investigation showed Congo red to have approximately the same properties as lissamine green thus belonging to the long series of vital stains staining like rose bengal merbromine eosin scarlet red bromothymol blue trypan blue and methylene blue

Congo red stains mucous fibrils and dead or degenerate cells Rose bengal stains also cells that are less degenerate than those stainable by Congo red In general rose bengal or lissamine green is therefore preferable not to miss pathological staining (keratinized cells in vitamin A deficiency desiccated cells in keratoconjunctivitis sicca pressure damaged cells due to ill fitted contact lens etc)

Fluorescein has quite different vital staining properties This dye penetrates into epithelial fissures thus staining epithelial lesions Congo red and fluorescein stain different elements and therefore supplement each other

However Congo red has two properties which the rose bengal group does not possess It is a pH indicator and it stains amyloid dichromatically in polarized light

In a previous study (Norn 1968) I estimated the acidity of cornea conjunctiva mucous thread and tear fluid after vital staining with bromothymol blue I found the pH to be $\leq$ 7 0 in most cases In previous literature a more alkaline value has been stated because no attention was paid to loss of carbonic acid

The pH range of bromothymol blue (6 8–7 6) lies however at such a relatively alkaline level that we cannot establish the limit towards the acid side The present investigation showed that acidities below the pH range of Congo

red (3 0–5 2) never exist in the region An indicator with a pH range closer to that of neutrality is therefore desirable for future examinations of the region

Polarizing red green dichroism specific of amyloid was detected in the mucous thread in the inferior conjunctival fornix The phenomenon seemed however to be due to degenerate mucous fibrils and not to amyloid

Such fibrils were seen particularly in cases of bacterial infectious conjunctivitis in other words the same clinical state in which I had previously found polarizing mucous fibrils on a mucous thread stained *in vitro* by toluidine blue (red in 84 per cent and green as well in 9 per cent) Further polarisation has been noticed in mucous threads stained by alcian blue and eosin (Norn 1969)

It is therefore to be supposed *that* the observed amyloid reaction indicates degeneration of mucous fibrils *that* it has nothing to do with proper amyloid but *that* the phenomenon is an important histological one of value in the differential diagnosis

In ordinary clinical practice Congo red is hardly indicated for vital staining of cornea and conjunctiva For this purpose fluorescein combined with rose bengal or lissamine green is still preferable because these combinations are capable of disclosing the greatest number of pathological phenomena

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EXAMINATION OF COLOUR VISION BY USE OF INDUCED CONTRAST COLOURS

Design of a New Series of Tissue Paper Contrast Tests

BY

EGILL HANSEN

The ability to induce contrast colours is evident in normal persons by the tissue paper contrast principle However tests of good quality are not easily available
The design of a new series of charts follows two principles 1) Selection of background hues in accordance with the maximally desaturated regions of the spectrum as seen by the colour defectives 2) Exact adjustment of the neutral test field (constituted by the chart figures) in order to eliminate any false clue due to brightness contrasts By introducing chart figures of alternative grey values appropriate tests can be attained for each type of colour vision defect
37 persons with congenital colour defects and 15 persons with acquired defects were examined The charts according to the criteria for selection proved to be selective in their screening efficiency

Key words simultaneous colour contrasts – brightness contrasts – intrinsic saturation of colours – congenital colour defects – acquired colour defects

Meyer discovered in 1855 that grey stripes across a coloured surface could be seen with a distinct contrast colour when covered with tissue paper The phenomenon has been utilized in tissue paper contrast tests the most successful

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of which was the Cohn s test chart (1905) Later on some charts based on the same principle have been included in the Velhagen s edition of the Stilling test (21st ed 1952) though with a design of less perfect quality Tissue paper contrast tests are valuable auxiliary tests in the evaluation of congenital colour defects as well as acquired colour defects (Hansen 1963 1976)

The purpose of this article is to describe a new series of tissue paper contrast charts the design of which is based upon the differences shown by colour defectives in their localization of maximum spectrum desaturation

Table I

Specification of the background colours and the neutral values of the figures used in the test charts

Test chart	Munsell notation		Dominant wave length (nm)	Neutral value of letters	
1 Blue	9 8 B	4 08/7 1	480	4 0	
2 Green	7 4 C	5 01/5 95	505	4 75	(a)
				5 5	(b)
3 Green yellow	5 1 GY	6 05/8 05	566	6 0	
4 Red purple	5 3 RP	3 96/8 4	500 C	3 75	(a)
				4 2	(b)
5 Red	2 4 R	4 14/9 5	660	3 5	(a)
				4 0	(b)
				4 5	(c)
6 Yellow red	7 6 YR	6 00/9 7	585	5 75	(a)
				6 0	(b)
7 Blue green	5 4 BG	4 92/7 2	492	4 5	(a)
				5 25	(b)
				5 75	(c)
8 Violet	2 5 P	5 01/9 4	67 C	5 0	
9 Grey		5 0		3 75	(a)
				4 25	(b)
				4 75	(c)
				5 25	(d)
				5 75	(e)
				6 25	(f)

Material and Methods

The material comprises 37 persons with congenital colour vision defects (11 protans 23 deutans and 3 achromats) and 15 patients with acquired colour defects The performance of 11 elderly normal persons (58 to 72 years of age) *was also registered The classification of the colour defects was based on* anomaloscope examinations

The new series consists of 8 coloured charts and 1 neutral grey chart The Munsell *colour sheets constituting the backgrounds* were selected in accordance with the indications of maximally desaturated hues as seen by the colour defectives (Chapanis 1944 Judd 1945 1949 Walls & Heat 1956) In that respect the design of the present test follows the same principle as was used in the AO H R R test (Hardy et al 1954) and approximately the same set of hues were selected for the charts Table I indicates the Munsell notation of the background colours as well as their dominant wave lengths The red purple (complementary to green at λ = 500 nm) and the blue green at λ = 492 nm are supposed to be appropriate for testing deutans and protans respectively Walls & Heat (1956) found the neutral point for protanopes at λ = 491–495 nm and in the region of λ = 496–502 nm for the deuteranopes Massof & Bailey (1976) found that the deuteranopic achromatic points had a still larger variability (495 to 505 nm) Our green chart of dominant wave length at λ = 505 nm is therefore *just on the border of the ideal value* The red at λ = 660 nm being complementary to the blue green at λ = 492 nm is supposed to be a good choise for protans The green yellow at λ = 566 nm and the violet being complementary to λ = 567 nm are quite near the achromatic point of tritanopes at about λ = 568 nm (Judd 1949) The blue and the yellow red charts like the corresponding figure hues in the AO H R R test are supposed to be appropriate for testing tetartanopes

Variation of the grey value of the figures in the new series of charts was obtained by cutting E letters out of the colour sheets and by placing the sheets over various grey surfaces The charts were then covered by tissue papers *The E letters* are of the same size as used in the Cohn s test (measuring 10 mm in square) An important point was to find the neutral value of the letters that could give the best possible brightness match with the coloured papers for each type of colour defectives An empirical approach was used by asking colour defective persons to match the colour sheets with a neutral grey scale and choose the possible matching pairs 6 protans and 11 deutans could do matches in that way Only a few tritan defectives of acquired type could be found for choosing such matching pairs As a result it was found that the protans required a dark grey to match the red colour and a bright grey to

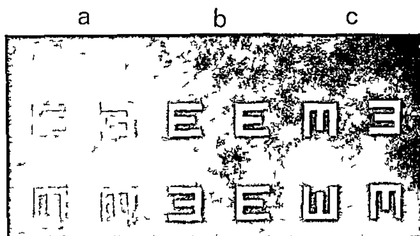


Fig 1
Black and white reproduction of chart 7 (blue green) showing 3 grey values of the chart figures

match the blue green colour both of which differed from those of the deutans Therefore in the second version of the test there may be 1 2 or 3 different grey values of the E figures on the same colour chart (Fig 1) Some patients have been examined with the first version only having one grey value of the E letters on each chart (indicated by a)

When covered by tissue paper the charts are still readable to normal observers without being too distinct (charts 5 and 6 with the most distinct letters were covered by double layers of tissue paper) The patients were asked to point out the direction of the E letters on each chart All the test charts as well as the other pigment tests were seen under artificial illumination from 2 Macbeth lamps (source C) giving approximately 300 lux Correction for near vision was used when necessary

Other colour vision tests

The AO H R R test comprises 14 charts for red green defectives and 6 charts for blue yellow defectives The performance on those charts as well as on 8 charts (No 10–17) of the Ishihara test (11th edition) was registered The charts K1 K2 of the Velhagen Stilling test (21st edition) were used for testing contrast sensitivity to green and the charts K3 K4 to red Positive sensation of heightened contrast sensitivity was indicated by the number of charts seen with such contrasts With the Farnsworth s D 15 test the typical confusion

Table II

The performance of 11 protans and 3 achromats with the new series of tissue paper contrast charts compared with other tests

Chart	*Top score*	P	EPA	PA	*Top score*	P	EPA	PA						Achromats		
B 1	8	5	8	8	8	8	8	6	8	8	8	8	8	6	7	8
G 2 a	8	4	8	8	4	4	–	2	3	3	4	3	4	2	1	2
b					4	4	–	–	4	2	3	–	2	–	–	–
GY 3	8	8	8	8	8	8	8	8	8	8	8	8	8	–	–	1
RP 4 a	8	–	1	8	4	1	–	–	–	–	2	–	–	–	–	–
b					4	–	–	–	–	–	2	–	–	–	–	–
R 5 a	8	–	–	1	4	–	–	–	–	–	3	–	–	–	–	–
b					4	–	–	–	–	–	–	–	–	–	–	–
c					4	–	–	–	–	–	1	–	–	–	–	–
YR 6 a	8	–	6	8	4	4	4	2	1	4	4	4	4	–	–	1
b					4	2	3	–	–	1	4	4	3	–	–	–
BG 7 a	8	7	8	8	4	4	3	–	4	4	4	4	4	4	4	4
b					4	3	1	–	2	2	4	1	4	4	4	4
c					4	1	–	–	–	–	4	–	–	2	2	–
P 8	8	8	8	8	8	8	8	8	8	8	8	8	8	2	7	8
9 a					3	3	3	3	3	3	3	3	3	3	3	3
b					3	3	3	3	3	3	3	3	3	3	3	3
c					3	1	1	1	3	3	2	–	3	1	3	–
d					3	–	–	–	–	–	–	–	–	–	–	–
e					3	–	–	–	2	–	–	–	–	–	–	–
f					3	3	3	3	3	3	3	3	3	3	3	3
RP Cohn	8	–		–	8	–	–	–	–	–	–	–	–	–	–	–
H H R (r g)		–	6	10	14	6	3	4	7	6	11	4	6	–	–	
Ishihara				–	8	–		–	–	2	–				1	
Contrast/green			2	–				2	–	1	–	2	2			
Contrast/red			2	–				–	1	1	–	2	1			
FD 15		P	P			P	P	(P)	N–	N–		N		A	A	IR

Normal scores are indicated by numbers and no score by –
P = protanope EPA = extreme protanomalous and PA = protanomalous

Table III

The performance of 23 deutans with the new series of tissue paper contrast charts and some other tests

Chart		*Top score*	D		LDA				DA			*Top score*	D		LDA								DA					
B	1	9	7	8	6	7	7	8	9	8	8	8	9	5	8	8	8	5	9	8	8	8	8	8	9	7
G	2 a	9	–	–	–	–	–	9	5	–	9	4	–	–	–	–	–	–	1	1	–	2	2	–	–	2
	b											4	–	–	–	–	1	–	–	1	–	3	3	–	–	1
GY	3	9	9	8	7	8	9	8	8	8	9	9	9	8	9	9	9	9	8	8	8	8	8	8	9	8
RP	4 a	9	–	–	–	–	–	8	8	8	9	4	1	–	1	–	–	3	–	1	4	3	4	2	–	–
	b											4	–	–	–	–	–	2	–	–	3	3	4	–	–	–
R	5 a	9	2	7	3	5	6	8	8	7	8	4	3	4	4	3	4	4	2	4	4	4	4	4	4	2
	b											4	3	3	3	–	3	4	1	3	3	4	3	4	2	2
	c											4	4	3	4	1	3	4	1	3	4	4	4	4	3	1
YR	6 a	8	7	8	8	9	8	9	8	8	8	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	b											4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
BC	a	8	6	3	[illegible]	–	6	8	9	7	8	4	1	–	2	–	3	–	–	3	–	4	4	2	3	4
	b											4	3	–	–	–	2	4	–	4	–	4	4	2	1	1
	c											4	4	4	4	–	4	4	4	4	4	4	4	4	4	4

1 8	5	9	5	7	8	8	9	9	8	8	5	9	9	8	9	6	9	8	8	8	8	8	8	8	9
9 a											3	9	3	3	3	3	9	3	3	3	3	9	3	3	3
l											3	9	3	3	9	2	3	9	3	3	3	3	3	3	3
c											3	2	1	1	1	–	1	–	3	–	3	2	3	3	1
d											3	–	–	–	–	–	–	–	–	–	–	–	–	1	–
e											3	–	–	–	–	–	–	–	–	–	–	–	–	–	–
f											3	9	3	3	3	3	9	9	3	3	3	3	3	3	3
RP Cohn	9	–	–	–	–	–	9	8	–	7	9	2	2	2	–	–	1	1	7	5	4	5	3	–	2
H H R (r g)		6	4	4		9	14	14	12	14	14		1	5	9	6	9	9	6	12	12	13	4	5	9
Ishihara		–		–		–	8	7			8						–		–	–	5	2	1		–
Contrast/green			–		–	1	–	–	–	–				1	2	–	–		2		–	–	2	–	–
Contrast/red			–		1	1	–	–	–	–				1	2	–	–		9		–	–	2	–	1
I D 15		D		D	N	D				N			D		D				N–	N	N	N–	D		

Normal scores are indicated by numbers and no score by –
D = deuteranope LDA = extreme deuteranomalous and DA = deuteranomalous

Table II

The performance of 15 patients with acquired colour vision defects with the new ser[ies] of charts and other colour vision tests

Chart		Top score	Cone dystrophy	Batten's dis		Pituitary disease Top score				Optic atrophy		Retinitis pigm	Macular degeneration		Stargardt's disease		
B	1	8	4	,	–	8	,	8	–	4	7	8	–	8	8	8	8
G	2 a	8	2	–	–	4	2	4	–	–	–	4	–	4	1	–	–
	b					4	1	4	–	–	4	4	–	4	–	–	–
GY	3	5	–	8	–	9		8	,	6	–	6	–	5	8	8	9
RP	4 a	5	–	–	–	4	4	4	–	–	4	4	–	4	1	–	–
	b					4	4	4	–	–	4	4	–	4	–	–	–
R	5 a	8	–	–	–	4	4	4	–	4	4	4	–	4	1	4	4
	b					4	4	4	–	1	4	4	–	4	1	–	[illegible]
	c					4	4	4		–	4	4	–	4	1	–	3
YR	6 a	8	–	–	–	4	4	4	–	3	4	4	–	4	4	4	4
	b					4	4	4	–	2	3	4	–	4	3	4	4
BG	7 a	8	8	–	–	4	4	4	–	2	4	4	–	4	4	–	3
	b					4	4	4	–	1	4	4	–	4	4	–	1
	c					4	4	4	4	4	4	4	4	4	3	–	4
P	8	9	6	8	–	9	6	9	2	,	9	–	–	–	8	8	8
	9 a					3	3	3	3	3	3	3	3	3	3	3	3
	b					3	3	2	–	3	3	3	–	3	3	3	3
	c					3	–	–	–	–	–	2	–	–	–	–	3
	d					5	–	–	–	–	–	–	–	–	–	–	1
	e					3	–	–	–	–	–	–	–	–	–	–	–
	f					3	3	3	3	3	3	3	3	3	1	3	3
RP	Cohn	5	–	–	–	9	,	9	–	–	–	5	–	8	2	–	–
H H R	r g		6	1	3	14	13	14	?	8	4	13	7	13	9	6	4
	b y		5	4	5	6	6	6	4	6	4	1	2	5	6	6	5
Ishihara			–		2	9	5	6	–	1	4	5		,	1	–	–
FD 15			N	RG	N–		N–	N	N		N	T	T	T	N	IR	N
100 Hue			139	11	160		185		203					211 T	59		
F H			G B	G+ B–	G+ B–		G B–						G+ B–	G– B+	G+ B		G+ B–
Nagel (g r q)			0 8	A	0 9		1 1		EDA	1 1	0 9	0 8	0 8	0 9	0 5		0.5
Visual acuity			0 6	0 1	0 9		1 0	1 0	0 8	0 9	1 0	0 8	0 9	1 0	0	0 4	0°
Sex			F	F	M		M	F	M	M	F	M	F	F	M	F	F
Age			13	,	49		66	30	45	51	19	27	70	15	?4	9	11

patterns were recorded (N = normal IR = irregular RG = red green axis P = protan D = deutan T = tritan A = achromatic) If no prevailing axis was found with the 100 Hue test the error score only was indicated For the Farnsworth s tritan chart (F II) the perception of the blue square (B) and the green square (G) was indicated The results of the anomaloscope examination (Nagel type I) were indicated by the green red quotient or by the typical pattern of performance (A = achromatic settings EDA = extreme deuteranomaleous settings)

Results

All the elderly normal persons could read the charts correctly except for 2 persons who had one or two occasional errors on the charts 1 2 3 or 8

The performance of the colour defective persons is shown in Table II III and IV On chart 9 where the contrasts are due to brightness differences only the darker letters appeared sufficiently distinct for reading when they differed at least 0 75 Munsell values from the grey value of the background whilst at least 1 25 value difference was necessary for the brighter letters to be read There is thus a general trend which was also found for the normal persons that the letters being darker than the background were more easily seen through the tissue papers than the letters differing from the background in the brighter direction

Table II shows that the protan defectives had very few correct scores both on the red chart and on the red purple chart as well as on the Cohn s chart The green chart was not very efficient in revealing protan defectives The blue green chart was not efficient in its first version either The letters in this version had only one grey value (indicated by 7 a) and were evidently too dark However in the second version the brightest letters (indicated by 7 c) were quite efficient in revealing protans Some of the protans also had difficulties on the yellow red chart The performance of the achromats on the charts 1 2 7 and 8 confirms that the darker letters as seen by the achromats may give a false clue to the reading of the letters

Table III shows that the deutans were well revealed by the green chart except for the slightest affected persons The green chart was somewhat better than the red purple chart which was also efficient and the results here were quite parallell to those of the Cohn s chart The latter chart is known as an efficient test for congenital colour defectives (Hansen 1963) Only a few deutans were revealed by the blue green chart and still fewer of the deutans by the red chart

When compared with the other colour vision tests it was found that the protan and deutan defectives who could read the AO H R R test and the Ishihara test quite well also had few mistakes on the tissue paper contrast charts 3 deuteranomalous persons referred because of dubious colour vision made no mistakes on the AO H R R test and also passed the tissue paper contrast tests Heightened contrast sensitivity on the ordinary contrast charts (K1 K4 in the Velhagen Stilling test) was stated by 6 protanomalous and 7 deuteranomalous persons all of whom had a poor performance on the tissue paper contrast charts Good performance on the tissue paper contrast charts was found among the persons with a normal or near normal performance on the F D 15 test

Table IV shows the results of some patients with acquired colour defects One patient with cone dystrophy in the early stage (described as case 3 in Hansen et al 1976) was well revealed by the tissue paper contrast charts in spite of a normal performance on the F D 15 test and the anomaloscope It is interesting to note that the patient with Batten s disease could see the blue the green yellow and the violet charts only Consistent with this a good blue receptor response had been demonstrated in this patient by registration of Stiles functions The cases of pituitary disease and optic atrophy included some patients with very slight defects of the red green type The performance of the retinitis pigmentosa patient was good except for a single chart the violet one which could not be seen One patient with macula degeneration also missed only this chart Their tritan defect was confirmed by the F D 15 test The performance of the 4 patients with Stargardt s disease (2 of which were suspected cases) is consistent with a red green defect None of the patients with acquired defects indicated heightened contrast sensitivity on the ordinary contrast charts of the Velhagen Stilling test

Discussion

Correct reading of the tissue paper contrast tests is dependant on the ability to induce contrast colours It is concerned with the genuine contrast sensitivity which is a characteristic of normal colour vision (Engelbrecht 1955) Accordingly all the charts of the new series were read by the normal persons On the other hand the colour defectives except for the slightest affected demonstrated qualified misreadings on certain charts The protans tended to fail in the reading of the red the red purple and the blue green charts while the deutans were most efficiently revealed by the green and the red

purple charts The results obtained with the tissue paper contrast charts can be referred to the spectrum regions of maximum desaturation as seen by the colour defectives This illustrates that good intrinsic saturation of the inducing colour is also essential for the tissue paper contrast effect The tissue paper contrast charts of the new series have proved to be quite as sensitive in revealing colour defectives as the AO H R R plates and also showing the same selectivity as to the type of colour defects

An apparently heightened contrast sensitivity which is indicated by many anomalous trichromats is to be distinguished from the genuine contrast sensitivity (Engelbrecht 1955) Accordingly our patients indicating heightened contrast sensitivity on the ordinary colour charts had in general poor performance on the tissue paper contrast charts and conversely those with the best performance on the latter charts could not indicate any heightened contrast sensitivity

The ideal test chart presupposes the induction of contrast colours to be the only clue to the identification of the figures Therefore in the new series efforts have been taken to eliminate the false clue due to brightness contrasts Reduction of brightness contrasts to a minimum also is in favour of good colour contrast effect (Kirschmann 1891) As shown with the chart 9 rather small brightness contrasts may be sufficient for reading especially for the letters deviating in the darker direction Also illustrating this point were the results of the achromats who could see some of the test charts despite their lack of colour vision but owing to their peculiar spectral sensitivity Likewise the protans having low sensation of brightness in the red and a particularely high brightness sensitivity in the blue green could not be revealed by the blue green chart until supplementary neutral letters of brighter value were introduced in the second version

The tissue paper contrast tests are useful as supplementary tests especially in evaluating the mild and moderate colour defects They are comparable with the pseudo isochromatic tests as to efficiency but not much correlated with the anomaloscope examinations where greatly saturated colours are used This is evident from the results obtained by the patients with the acquired colour defects In these patients demonstration of poor induction of contrast colours to certain hues may be significant for the understanding of their fundamental defect An accurate specification of the colours of the test charts is then necessary

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ATROPHY OF OPTIC NERVE FIBRES IN COMPRESSION OF THE CHIASM

Degree and Distribution of Ophthalmoscopic Changes

BY

M LUNDSTRÖM and L. FRISÉN

Chiasmal lesions produce a characteristic form of partial optic atrophy subtly reflected by objective changes in the peripapillary portion of the retinal nerve fibre layer The degrees and distributions of these changes were documented by fundus photography in a series of steady state patients with different degrees of chiasmal damage from pituitary adenoma Semi quantitative analysis disclosed a close correspondence with the degree of functional deficit The state of the retinal nerve fibre layer can therefore be used as an objective indicator of the occurrence and severity of anatomical chiasmal damage

Key words optic atrophy – optic chiasm – pituitary tumour – visual field – ophthalmoscopy

Functional disturbances of the visual system due to compression of the optic chiasm have been documented extensively in the literature (e g Mackenzie 1835 Cushing & Walker 1915 Chamlin & Davidoff 1962 Verriest 1975) The most common deficit in chiasmal compression caused by a suprasellar mass is a bitemporal field defect In cases of chromophobe adenomas for instance bitemporal field defects occur in 80 to 96 per cent of the patients (Lyle & Clover 1961 Chamlin et al 1955)

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as detailed by Hoyt et al (1973b) We have shown elsewhere that these fun duscopic signs gradually disappear during the development of optic atrophy (Lundstrom & Frisen 1975) Mottling of the retina and so called pseudo sheathing of major vessels close to the optic disk appear secondarily A system for regional grading of diffuse atrophy of optic nerve fibres has been built on these observations In the present series of chiasmal lesions we have not found one single instance of focal nerve fibre defects as described by Hoyt and coworkers in glaucoma and optic nerve diseases (1973b 1974) Table I therefore deals with diffuse defects only

Distribution of peripapillary nerve fibre layer atrophy A mid chiasmal lesion will primarily engage optic nerve fibres from the nasal hemi retina These fibres course towards the optic disk from all directions Fibres from the tem

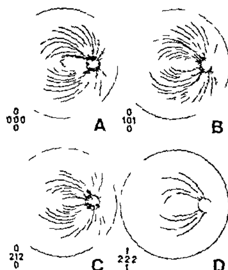


Fig 1

Schematic drawing of retinal nerve fibre bundles in four stages of progressive chiasmal damage The atrophy scores are derived from Tables I and II Interrupted lines re present nerve fibres serving the nasal hemi retina solid lines those serving the temporal hemi retina

A Normal eye

B Partial loss of nerve fibres that cross in the optic chiasm Atrophy is most obvious in the nasal and papillomacular bundles *resulting in score* 1 *in these areas* Summed atrophy score 2

C Total loss of crossing nerve fibres with exposure of nasal and temporal disk borders Summed atrophy score 5

D Partial atrophy also of non crossing nerve fibres Summed atrophy score 5

Table II
Degree and distribution of optic disk atrophy

Score	Signs
0	Optic disk borders finely blurred Optic disk with normal colour
1	Sharp nasal and temporal disk borders
2	*Sharp optic disk borders in all directions* Marked pallor of the optic disk

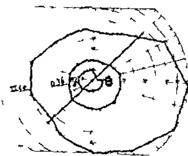
poral hemi retina reach the disk from above and below and intermingle with nasal fibres in these areas (Fig 1 A) We have graded the appearance of the peripapillary nerve fibre layer above below nasal and temporal to the optic disk

Degree and distribution of optic disk atrophy There is a great variation in the size of the optic disk and cup Grading of the disk colour is notoriously difficult The sharpness of the disk border is a less debatable sign Therefore the optic disk grading used here was based primarily on the definition of the borders of the optic disk (Table II)

Scoring of the degree of atrophy In order to grade the total optic nerve fibre atrophy we have added scores for the four nerve fibre loci and the optic disk

Table III
Grading of visual field defects in chiasmal compression

Score	Visual field defect
0	No visual field defect
1	Relative defect in one quadrant
2	Relative defects in two quadrants or absolute defect in one
3	Relative defects in three quadrants or absolute defects in two
4	Absolute defects in more than two quadrants



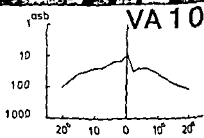
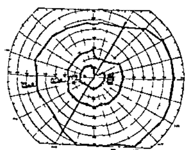


Fig 3

Case 2 Photographically reversed picture of the left fundus and visual field Consult the text for details



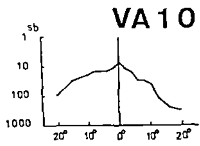
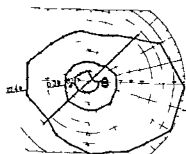


Fig 4
Case 3 Photographically reversed picture of the left fundus and visual field
Consult the text for details



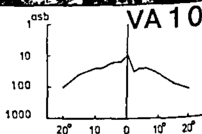
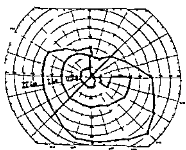


Fig 5

Case 9 Photographically reversed picture of the left fundus and visual field
Consult the text for details

0
202
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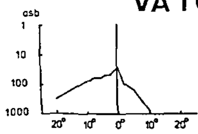
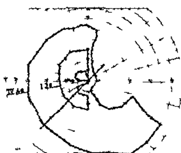


Fig 6
Case 5 Photographically reversed picture of the left fundus and visual field
Consult the text for details



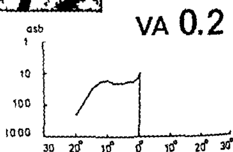


Fig 7
Case 6 Photographically reversed picture of the left fundus and visual field
Consult the text for details

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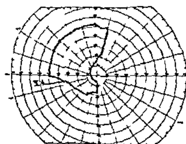


Fig 8
Case 7 Consult the text for details

5 Printer 65 with fatigue and failing potency during the last two years There were no visual complaints but visual field examination suggested a chiasmal lesion A supra sellar mass was seen on an air study Pre operative irradiation was carried out Surgery revealed a pre fixed optic chiasm distended from behind by the tumour The microscopic diagnosis was chromophobe adenoma

Four years following surgery visual acuity in the left eye was 1 0 (+2 0 ph) There was a predominantly relative upper temporal defect (Fig 6) score 2 There were no signs of nerve fibres in the temporal and nasal sectors score 2 The lower arcuate bundle was *hardly visible but obvious cross hatching still existed score 1* The upper arcuate bundle scored 0 There were no definite signs of atrophy in the optic disk although the temporal border seemed rather denuded scoring 0 Total score 5

6 Male shop keeper 69 six months history of impaired vision There were dense temporal field defects in both eyes An air study showed a 2 cm large mass above the sella At surgery the optic chiasm was lifted upwards by the tumour Microscopic examination showed chromophobe adenoma

The left eye was examined four months after surgery Visual acuity was 0 9 (+1 5 sph) There was a large temporal defect and a small lower nasal depression (Fig 7) score 3 There were no signs of nerve fibres in the nasal and temporal areas score 2 The nerve fibre pattern was very faintly visible in the arcuate bundles score 1 The optic disk had very well defined nasal and temporal borders scoring 1 Total score 7

7 Male workshop owner 28 poor vision in both eyes since at least two years Dense bitemporal field defects The third ventricle was displaced upwards in an air study A very large chromophobe adenoma was removed at craniotomy

Three years following surgery the visual acuity was *counting fingers* at 1 m in the right eye There was a pronounced field defect (Fig 8) score 4 The retina appeared almost denuded *from nerve* fibres except in the lower arcuate area scoring 2+2+2+1 The optic disk was uniformly pale and had very sharp borders (score 2) Total score 9

Discussion

The visibility of fundus detail is a function of size and contrast Single axons *from retinal ganglion cells fall below the resolution limits of both* ophthalmoscope and fundus camera (Frisen 1973) Bundles of axons have better visibility Because of the convergence of nerve fibres towards the optic nerve *head* prominence of nerve fibre bundles increases centripetally *in the fundus* and is maximal in the peripapillary area Visibility drops precipitously at the very margin of the optic disk because of the poor contrast between axons and disk glia axonal bundles are seldom if ever visible within the nerve head itself Prepapillary membranes constitute additional obstacles Because of these circumstances optic atrophy or loss of axons can be more accurately evaluated from the appearance of the peripapillary nerve fibre layer than

from the appearance of the optic disk (Hoyt and coworkers 1972 1973a b) Histopathologic proof that the changes seen in the nerve fibre layer represent loss of axons is available (Frisch et al 1974) The superior sensitivity of this novel method is well illustrated by the results from the present study Instead of the circa 50 % incidence of optic atrophy expected from reports by investigators using disk pallor as an end point it turned out that every single case *in our series presented objective signs in the peripapillary area of struc* tural damage to the anterior visual system

The different degrees and distributions of signs of nerve fibre damage documented here represent different stages of destruction of the anterior visual pathway The most discrete sign of damage was partial atrophy of nasal and papillomacular fibres These defects were seen only in eyes with minimal functional deficit With more advanced chiasmal damage there was a total atrophy of the nasal and papillomacular areas The disk borders were exposed in the same areas and there was some pallor in corresponding sectors sometimes suggesting a pale band across the disk Absolute temporal field defects occurred at this stage Some cases with strictly temporal field cuts also presented signs of partial atrophy of the arcuate bundles (Fig 6) Pronounced thinning of the arcuate bundles signified severe damage At this stage the disk borders were clearly exposed all around the circumference and there was uniform disk pallor The functional corollary was contraction of the remnant nasal visual field

Most commonly the degree and distribution of nerve fibre damage was the same in the upper and lower parts of the fundus This applies also to the stage in chiasmal compression where the field defect was most pronounced in the upper temporal area At this time we cannot offer an explanation for the different distributions of functional and anatomical damage On the other hand asymmetrical loss of nerve fibres was often seen at the stage where the nasal field was defective In this connection it is interesting to note that some of our cases with signs of wasting of both crossed and non crossed nerve fibres lacked nasal field defects This discrepancy indicates that a diffuse loss of neurones needs not affect visual function as tested in perimetry

A close relationship was found between visual field and atrophy scores in steady state patients (Fig 9) It must be emphasized however that such a well defined numerical relationship can be expected solely with fairly symmetrical chiasmal lesions The reason for this is the peculiar anatomy of the retinal nerve fibre layer A complete loss of fibres from the nasal hemi retina *results in a much higher* atrophy score than does a corresponding loss of nerve fibres from the temporal hemi retina (Fig 1) A regular progression in summed atrophy scores occurs only when damage proceeds from crossing to non

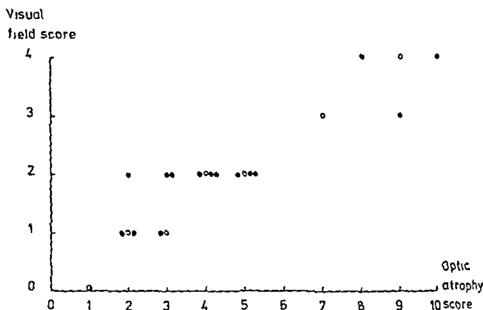


Fig 9

Relationship between degree of optic atrophy and visual field defect in 19 patients with steady state chiasmal lesions caused by chromophobe adenomas Each observation represents one eye Open circles identify cases described in detail

crossing fibres It must also be emphasized that patients with *on going* chiasmal compression may deviate from the steady state scheme outlined above in that their functional deficit may be due to a combination of reversible conduction failure and irreversible anatomical damage As a matter of fact vision is usually more severely affected than the nerve fibre layer in these cases The prognostic implications of such a discrepancy will be dealt with separately Another limitation applies to the considerable delay between the time of actual damage and the time when visible nerve fibre changes occur in the fundus (Lundstrom & Frisen 1975) An irreversible lesion in the region of the chiasm will not produce funduscopic signs of atrophy until at least four weeks later

Scoring the degree of atrophy was as easily done by ophthalmoscopy as by studying fundus photographs We never differed by more than one point in our summed atrophy scores proving that experienced examiners agree closely in their evaluation A detailed analysis of accuracy and precision is presently under way An objective scoring technique is also being evaluated (Lundström & Eklund in prep) Documentation of the changes in the retinal nerve fibre layer described here is facilitated by a widely dilatated pupil clear

media good fundus pigmentation and precise focusing A red free filter is also advantageous In a clinical series like ours there is a great variation in the transparency of the optic media We therefore preferred a wide band low density filter in combination with a 400 ASA film Image contrast can be further enhanced in many ways (Frisen & Hoyt 1973) The double reproduction method used here raises contrast adequately and is uniquely simple in use There is minimal need for cooperation in the present method of evaluating the state of the anterior visual pathways There is no need to detail its advantages in the examination of children and obtunded patients

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VOGT s RETRO IRIDIAN PIGMENT LINES

Light Microscopical and Ultrastructural Study of a Case

BY

F ERLIN LARSEN and J HVIDBERG

A woman aged 69 with latent diabetes was found to have retro iridian pigment lines Cataract extraction was followed by light microscopy and electron microscopy Cross sections of the pigment lines showed these to consist of two main constituents whose structures are described The portion of the lines closest to the lens had a certain resemblance to the substance seen on the lens and in the iris in pseudo exfoliation, while the remaining part of the pigment lines consisted of uniform microtubules

Key words retro iridian pigment lines – iris pigment – lens – lens capsule – pseudo exfoliation – electron microscopy – diabetes

Vogt in 1921 described and depicted characteristic radially arranged pigment lines on the anterior lens surface Such lines have since borne his name As far as we know the literature contains no description of the histology of these lines In the present paper we report the results of examinations of the anterior lens surface and the iris pigment epithelium of a diabetic who on slit lamp examination exhibited both cataract and typical pigment lines

Received June 11 1976

Material

Case Report

A woman aged 59 was admitted to hospital for cataract extraction Glycosuria had been detected 10 years previously but a diabetic diet had been the only antidiabetic treatment required The patient had otherwise always been in good health

The patient's eye complaints had been present for about two years with gradual visual impairment of the left eye On admission a dense posterior cortical catarat was noticed in the left eye and incipient cataractous changes in the right Both eyes had normal corneas and medium deep chambers with no aqueous flare Both eyes had blue irides with mild atrophy of the peripupillary pigment epithelium but no rubeosis or flocculi The other part of the iris pigment epithelium was not pellucid A discrete network was noticed representing remnants of a persistent pupillary membrane On both anterior lens surfaces we found thin linear radial pigment lines as illustrated in the diagram (Fig 1) The greatest number of lines were situated nasally Despite examination with maximum mydriasis no signs of pseudo exfoliation were seen Visual acuity was normal in the right eye whereas it was reduced to finger counting in the left eye

The tension was normal in both eyes 13 and 14 mmHg appl in right and left eye respectively

Ophthalmoscopy which could be performed in the right eye only showed tig oid markings but was otherwise normal more especially there were no diabetic changes The vitreous body was collapsed

Cataract extraction was performed with a corneoscleral opening under a limbus based conjunctival flap After sector formed iridectomy the lens was extracted by means of a cryostylet applied superiorly on the lens The anterior lens surface was not

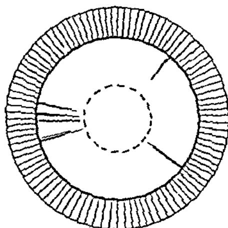


Fig 1
Diagrammatic illustration of the location of the pigment lines on the anterior surface of the left eye

touched during the operation The postoperative course was uneventful except for a short period when tension was raised

At control examination four months later the operated eye was satisfactory with a *normal visual acuity* The *pigment lines* previously observed in the non operated right eye were found to have decreased in number Otherwise the control examination was unchanged

Analysis of the urine disclosed no excretion of sugar The blood sugar was likewise normal but a glucose tolerance test showed definitely abnormal values

Method

Immediately after withdrawal of the lens and the iris biopsy specimens they were transferred to cacodylatebuffered 4% glutaraldehyde at 4 C After the anterior lens surface had been examined under an operation microscope the anterior parts of the lens were cut into sections 1 x 1 x 1/4 mm in size These were re fixed for 24 h in 4% glutaraldehyde at 4°C and then post fixed in osmium tetroxide for 30 min at 4 C Finally after dehydration in acetone 25–100% they were embedded in araldite Standard sections one micron thick were subjected to light microscopy after staining with toluidine blue and in the cases of the lens sections with periodic acid Schiff and periodic acid silver methanamine (Cardno & Steiner 1965) the former with and without counterstaining with toluidine blue Normal conjunctival tissue was examined in the same manner by way of control Electron microscopy was performed in a JEM T 7 and a JEM A 29 microscope with subsequent photographic magnification The tissue was embedded so as to be cut at right angles to the course of the lines The iris biopsy specimen was embedded in the same manner and cut at right angles to the posterior iris surface

Results

On examination under an operation microscope the extracted and partially fixed lens revealed no remarkable changes of the peripheral part which had previously been covered by the iris In several regions the pigment lines observed with the biomicroscope had not been damaged by the extraction These regions were further examined

At the sites of the transected pigment lines light microscopy disclosed some rounded formations situated on the anterior lens surface (Fig 2) These formations could be followed in serial sections through the block They were seen to be located at intervals corresponding approximately to the clinically observed intervals between the lines The cross sections showed that the substance of the *pigment lines could* be classifiable into two main constituents A homogeneous cylindric and locally pigmented substance described below as the main substance

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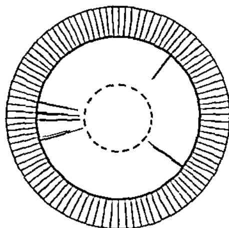


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Fig 4
Varieties of pigment lines Both show a canal like structure in the main substance (x 5800)

found to contain vesicles membrane debris and other cell débris like particles

As for the fine structures of the main and the capsule near substances reference is made to Figs 7 and 8

The lens epithelium was examined over an area corresponding to the site of the pigment lines i e a region of the anterior lens surface between 2 0 and 3 5 mm from the centre of the lens The capsule presented a normal structure (Fig 5) and its thickness was measured at 20 microns We found no amorphous layer like that described by Bertelsen Drablös & Flood (1964) in cases of epitheliocapsular fibrillopathy We did not however study the structure of the capsule outside the above mentioned region i e not along the boundary of the lens epithelium

On the fine structural plane the lens epithelium showed somewhat unsatisfactory fixation as judged from the appearance of the organelles and in particular the mitochondria

In the epithelial cells 10 microns tall we found irregular vacuoles containing fibrillar and here and there laminar material (Fig 5)

The part of the lenticular cortex situated immediately under the epithelium contained lens fibres of varying electron density

The structure of the iris pigment epithelium was normal (Tousimis & Fine 1961 Hvidberg Hansen 1973) However the lateral interdigitations were only slightly developed and pigment attenuated cells showing signs of glycogen



Fig 5
Araldite embedded 1 micron section Light microscopy Section of lens capsule seen with normal configuration A somewhat disintegrated pigment line contains a melanosome aggregation Irregular vacuoles are seen in the epithelial cells (arrows) (× 2800)

accumulation were present (Fig 6 a + b) These phenomena are characteristic of diabetics (Hvidberg Hansen 1973) We observed no unquestionable disintegration of the pigment granules in the pigment epithelium Such may likewise be seen in diabetics

A deviation from the normal appearance was noticed within a minor area of the basal membrane covering about 20 cells At this site the basal membrane was irregularly thickened and locally duplicated (Fig 6 a) Except for the presence of isolated pigment granules (Fig 6 b) the structure of the abnormal basal membrane bore no resemblance to the main substance of the pigment lines The structure was more like that of the capsule near substance It is worth pointing out that a substance corresponding to that seen in epithelio capsular fibrillopathy was neither detected in on nor under the basal membrane (Ringvold 1970)

Discussion

Bruckner (1907) was probably the first to describe the pigment lines which have since become universally known from Vogt s slit lamp atlas (1921 1931)

Some clinical descriptions have been published (Lugli 1933 Streiff 1935 Bischler 1939) Of the 39 patients described 29 were females and all the patients were aged over 40 years

Ohrt (1967) examined 122 diabetics and found pigment lines in 20 per cent. Out of 110 non diabetic patients no more than 3 per cent presented this anomaly

The pigment lines appear as very fine strictly linear, most often brown or yellowish brown lines located on the anterior lens surface within the area of movement of the pupillary margin They are variable in length but most often *3–4 mm long They are generally concentrated in groups but may also occur* singly There is a definite tendency towards accumulation on the nasal part of the lens A small number of the lines may be ramified and if so generally with bayonet formed bends When lying close together the distances appear uniform The lines may disappear within periods ranging from af few days to months Our case displayed the typical clinical picture though without ramifications The inconstancy of the lines was also observed in our case A relationship is likely to exist between presence of pigment lines and diabetes but



Fig 6a

Section through the iris pigment epithelium towards the posterior chamber showing duplication and wrinkling of a basal membrane of normal thickness (× 24 000)

otherwise the aetiology is obscure The early writers (Vogt and Lugli) judged the lines to be remnants of the vascular capsulo pupillary membrane Vogt having seen continuity of the lines and fibres of persistent pupillary membrane Our patient presented both pigment lines and remnants of a persistent pupillary membrane but there was no continuity

Bischler Streiff and Ohrt maintain that the lines originate from the iris pigment epithelium which often shows defects along the pupillary margin off

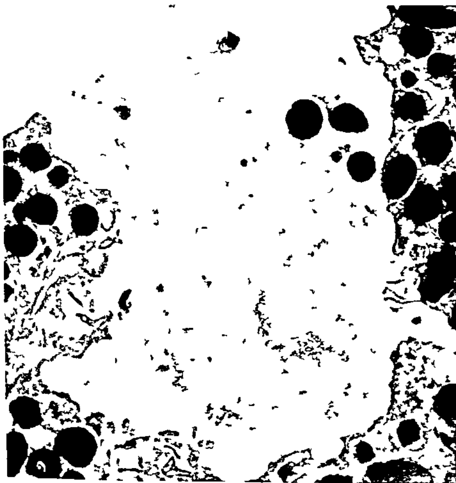


Fig 6 b

Groove of the pigment epithelium filled in by an abnormally thickened basal membrane Detached pigment granules are seen cf Fig c (24 000)

the course of the lines In a small number of cases pseudo exfoliation has been observed concurrently with linear formation on the lens surface (Bischler Vogt and Moller)

Our studies disclosed the structures of the lines in transverse and tangential sections However this did not clarify the aetiology Pigment lines were lost during the lens extraction and we therefore did not have enough lens material with such lines at our disposal for paraffin embedding with a view to light microscopy and classical histochemical analysis

Our investigation gave the result that the pigment lines must consist of the

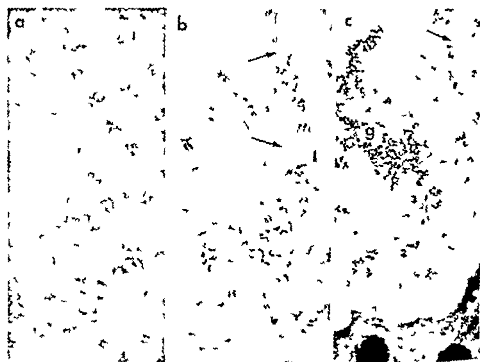


Fig 7

a Detail of main substance The individual elements display a tubular structure All the tubules have a diameter of 10 nm but beyond that no indisputable regularity of structure was demonstrable (× 370 000)

b Detail of capsular near substance A fibrillar arrangement is seen with no unquestionable cross banding of the longitudinally cut fibres (arrows) A certain resemblance is noticeable however to pseudo exfoliation material (×49 000)

c Detail of abnormal basal membrane on the posterior iris surface Glycogen like particles (g) are seen both intracellularly and in the thickened basal membrane Further cell debris (arrow) are seen (×48 000)

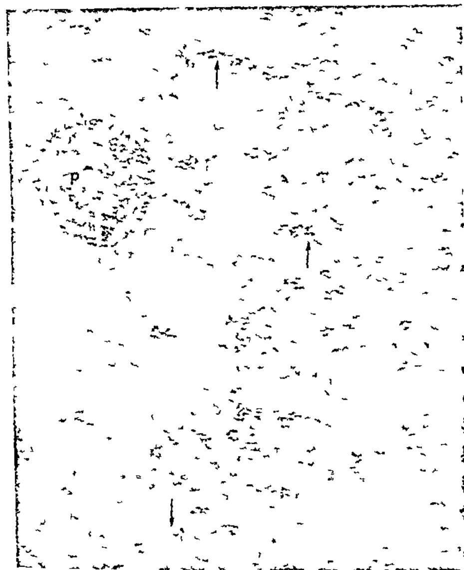


Fig 5
Detail of main substance with obliquely cut tubules (arrow) An immature pigment granule (p) is seen No cross banding of the tubules is observable (× 3 0 000)

two substances mentioned above Of these the capsule near substance bears a fairly strong resemblance to the abnormally thickened basal membrane of the posterior iris surface seen in Fig 6 b in a groove of the pigment epithelium Note that the normal basal membrane is continuous with the distinctly changed one We cannot say for certain whether this groove corresponded to the course of a pigment line The capsule near substance is reminiscent in appearance of the fibrillar material in pseudo exfoliation (Ringvold 1970) The lens capsule displayed no signs of exfoliation within the examined area

The main substance consists of tubules running longitudinally and having a uniform diameter of about 1 nm (Fig 7 a) We have been unable to establish the exact nature of these tubules Pigment granules were present in a surprisingly small number They had the character of the pigment of the iris epithelium and must be supposed to originate from this The accumulation of pigment as seen in Fig 5 may explain the pigment aggregations on the lines visible with the slitlamp

The origin of the pigment lines is difficult to clarify on the basis of their morphology Even though the main substance has a lumen we are not inclined to believe that it bears any relation to the foetal vascular capsulo pupillary membrane The radial arrangement corresponds exactly to the movements of the iris over the lens and it is a well known fact that diabetics have an increased pigment liberation The pigment deposition may therefore be a secondary phenomenon

Addendum

After acceptation of this paper for publication G D Sturrock & R C Tripathi (*Brit J Ophthal 60* 25i–293 1976) have published seven cases of Vogt s retroiridian pigment lines with electron *microscopy*

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THE CYCLOPENTOLATE PROVOCATIVE TEST IN SUSPECTED OR UNTREATED OPEN ANGLE GLAUCOMA

III The Significance of Pigment for the Result of the Cyclopentolate Provocative Test in Suspected or Untreated Open Angle Glaucoma

BY

OLAVI VALLE

Significant elevations of IOP i e responses occurred in eyes with suspected or untreated open angle glaucoma during the mydriasis test with 1 % cyclopentolate (CPT) The possible role of pigment in the IOP elevations seen in the responders was studied
Pigment was liberated in the aqueous sometimes very profusely in 68 (31 9 %) of 2 6 eyes during CPT The maximal IOP elevations ad 20 mmHg were seen in just these eyes They were eyes with capsular or pigmentary glaucoma or eyes in which exceptionally heavy pigment was demonstrated in the chamber angle for other reasons There was a statistically significant correlation between pigment liberation and IOP elevation during CPT Evidently profuse pigment liberation may have caused transient blocking of the trabecular meshwork obstruction of aqueous outflow and elevation of IOP
Liberation of pigment in the aqueous during CPT was statistically highly significantly more profuse in eyes with pseudoexfoliation than in eyes without pseudoexfoliation An equally significant correlation was demonstrated between the grade of chamber angle pigmentation and the degree of pigment liberation during CPT
The significance of pigment for IOP elevation was seen also in the statistically highly significantly more profuse pigmentation of the chamber angle in the responder than in the *non responder* eyes

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Key words cyclopentolate – intraocular pressure – mydriasis provocative test – open angle glaucoma – pigmentation of chamber angle – pigment liberation – pseudoexfoliation – suspicion of open angle glaucoma

The role of pigment in eyes with open angle glaucoma has aroused the interest of researchers for a long time In 1921 Kollner performed the mydriasis provocative test on 13 eyes with simple glaucoma using atropine homatropine or scopolamine for it In one eye profuse pigment was liberated in the aqueous after the homatropine administration and intraocular pressure (IOP) rose by 10 mmHg There was exceptionally heavy pigment in this eye on the iris the posterior surface of the cornea and in the chamber angle (pigmentary glaucoma?) The IOP did not rise during the test in the other eyes Vogt (1925) Pillat (1934) and Bard (1935) observed in some eyes with pseudoexfoliation and glaucoma profuse liberation of pigment in the aqueous in connection with mydriasis Marked liberation of pigment in the aqueous during mydriasis has been frequently seen in the same way in eyes with Krukenberg s spindle and atrophy of the pigment epithelium of the iris (Tarkkanen 1962) These studies do not mention IOP in association with mydriasis and liberation of pigment Very notable elevations of IOP during the mydriasis test have been observed in patients with pigmentary glaucoma (Sugar & Barbour 1949 Malbran 1957 Etienne & Pommier 1957 Kristensen 1965) Certain other investigators (Calhoun 1953 Kjer 1961) have not been able to establish this

Mitsui & Takagi (1961) reported liberation of pigment in the aqueous humour of the anterior chamber in 4 6 % of 948 eyes after administration of 5 % phenylephrine The amount of pigment granules in the anterior chamber was at its maximum 1–3 h after the beginning of the test and the floaters disappeared completely within 12–24 h Pigment liberation has been demonstrated particularly in elderly subjects (Mitsui & Takagi 1961 Kristensen 1965 Haddad et al 1970 Aggarwal & Beveridge 1971 Krause et al 1973) It was seen in 30 % of patients aged over 80 in 3 % of those under 50 and in none of the patients under 30 years (Mitsui & Takagi 1961) Kristensen (1965) observed liberation of pigment in 79 % of healthy eyes after the administration of sympathomimetics Some pigment was always liberated in glaucomatous eyes after long term miotic therapy owing to atrophy of pigment cells and accumulation of pigment in the iris during the reduced pupillary motility (Kristensen 1965) Parasympatholytics cause pigment liberation in the aqueous less frequently than sympathomimetics in the same persons (Mitsui & Takagi 1961) They found the size of the granules to be 1 0–1 5 μ The granules matched the pigment granules of pigment epithelium of the iris in colour size and shape When the dilatator muscle contracts the pigment epithelium of the iris also

Table II

Degree of pigment liberation in aqueous humour during the cyclopentolate provocative test (Mitsui value) and correlation with the concomitant change in IOP in 276 eyes with suspected or untreated open angle glaucoma

Result of the CPT	Degree of pigment liberation							No of eyes	Mean Mitsui value
	0	1	2	3	4	5	6		
Non responders (rise of IOP $\leq$ 4 mmHg)	165	35	5	13	6	8	1	233	0.66
Borderline (rise of IOP = 5–7 mmHg)	18	4	2	2	0	2	0	28	0.86
Responders (rise of IOP $\geq$ 8 mmHg)	5	1	1	2	0	1	5	15	[illegible]93*
No of eyes	168	40	8	17	6	11	6	276	0.80
%	68.1	14.5	2.9	6.1	2.2	4.0	2.2	100.0	

Chi square test
(χ^2 = 12.86)

* The difference is significant at $P < 0.01$

Table III

Degree of pigment liberation in aqueous humour (Mitsui value) during the cyclopentolate provocative test in 276 eyes with or without pseudoexfoliation

	Without pseudo exfoliation	With pseudoexfoliation			
		+	++	+++	Total
Mean Mitsui value	0.58	1.38	1.70	[illegible]33	1.71
(± SD)	(± 1.38)				(± 1.[illegible])
No of eyes	221	16	30	9	55

Kolmogorov Smirnov two sample test D - 0.442
* The difference is significant at $P < 0.001$

Key words cyclopentolate – intraocular pressure – mydriasis provocative test – open angle glaucoma – pigmentation of chamber angle – pigment liberation – pseudoexfoliation – suspicion of open angle glaucoma.

The role of pigment in eyes with open angle glaucoma has aroused the interest of researchers for a long time In 1921 Kollner performed the mydriasis provocative test on 13 eyes with simple glaucoma using atropine homatropine or scopolamine for it. In one eye profuse pigment was liberated in the aqueous after the homatropine administration and intraocular pressure (IOP) rose by 10 mmH There was exceptionally heavy pigment in this eye on the iris the posterior surface of the cornea and in the chamber angle (pigmentary glaucoma?) The IOP did not rise during the test in the other eyes Vogt (1925) Pillat (1934) and Bard (1935) observed in some eyes with pseudoexfoliation and glaucoma profuse liberation of pigment in the aqueous in connection with mydriasis Marked liberation of pigment in the aqueous during mydriasis has been frequently seen in the same way in eyes with Krukenberg s spindle and atrophy of the pigment epithelium of the iris (Tarkkanen 1962) These studies do not mention IOP in association with mydriasis and liberation of pigment Very notable elevations of IOP during the mydriasis test have been observed in patients with pigmentary glaucoma (Sugar & Barbour 1949 Malbran 195, Etienne & Pommier 1957 Kristensen 1965) Certain other investigators (Calhoun 1953 Kjer 1961) have not been able to establish this

Mitsui & Takagi (1961) reported liberation of pigment in the aqueous humour of the anterior chamber in 4 6 % of 948 eyes after administration of 5 % phenylephrine The amount of pigment granules in the anterior chamber was at its maximum 1 3 h after the beginning of the test and the floaters disappeared completely within 12–24 h Pigment liberation has been demonstrated particularly in elderly subjects (Mitsui & Takagi 1961 Kristensen 1965 Haddad et al 1970 Aggarwal & Beveridge 1971 Krause et al 1973) It was seen in 30 % of patients aged over 80 in 3 % of those under 50 and in none of the patients under 30 years (Mitsui & Takagi 1961) Kristensen (1965) observed liberation of pigment in 79 % of healthy eyes after the administration of sympathomimetics Some pigment was always liberated in glaucomatous eyes after long term miotic therapy owing to atrophy of pigment cells and accumulation of pigment in the iris during the reduced pupillary motility (Kristensen 1965) Parasympatholytics cause pigment liberation in the aqueous less frequently than sympathomimetics in the same persons (Mitsui & Takagi 1961) They found the size of the granules to be 1 0–1 5 μ The granules matched the pigment granules of pigment epithelium of the iris in colour size and shape When the dilatator muscle contracts the pigment epithelium of the iris also

contracts and this may cause rupture of degenerated pigment cells and liberation of pigment granules in the aqueous The result in extreme cases may be an increase in aqueous viscosity and cessation of the circulatory stream of the aqueous humour (Mitsui & Takagi 1961)

After administration of 10 % metaoxedrin Kristensen (1965) observed a pathologic elevation of IOP (22 → 46 mmHg 27 → 45 mmHg and 12 → 27 mmHg) in one eye and concurrently marked liberation of pigment in the aqueous humour in two patients with capsular and one patient with pigmentary glaucoma whose chamber angles were open and heavily pigmented He thought it plausible that the rise in IOP was caused by transient blocking of the trabecular meshwork by the heavily liberated pigment In another material Kristensen (1968) using sympathomimetics established marked pigment liberation of grade 5–6 in as many as 82 of 97 eyes with open angle glaucoma IOP rose concomitantly ≧ 8 mmHg in 47 eyes

The present paper is a part of a project to study the effect of 1 % cyclopentolate on IOP in patients with new previously untreated or suspected open angle glaucoma Part I of the study (Valle 1976) presented the investigation plan as a whole the material methods and criteria and the results of the effect of the cyclopentolate provocative test (CPT) on IOP in these patients Eyes in which significant elevations of IOP i e responses (≧ 8 mmHg rise in IOP) were observed during the mydriasis test were the object of especial interest Part II of the sutdy (Valle 1976) analysed in particular the responders group and reported other investigation results and clinical findings to obtain additional information on the mechanism of IOP elevation in responders It appeared that the biggest group among the responders – 48 % – consisted of eyes with pseudoexfoliation and open angle glaucoma It is well known that such eyes display considerable pigmentation changes (e g Duke Elder 1969 Aasved 1973) The aim of the present study was to clarify the potential role of pigment in the IOP elevations seen in the responders

Material Methods and Criteria

The patients and the methods and criteria used in the study were the same as those detailed in Part I (Valle 19 6) The classifications of the occurrence of pseudoexfoliation or cataract and the changes in the optic discs and visual fields were reported in Part II (Valle 1976)

Liberation of pigment in the aqueous humour during cyclopentolate provocative test (CPT) was studied in 276 eyes using the method and system of grading introduced by Mitsui (1943 1961) (Table 1) The biomicroscopy for the evaluation of the liberation of pigment was performed with a Haag Streit 900 slit lamp using the following

Table I
Grading of floaters following mydriasis (after Mitsui 1961)

Grade	Number of floaters
0	No floaters
1	One to several floaters in the whole aqueous
2	One to several floaters in one section of beam
3	About ten floaters in one section of beam
4	Several tens of floaters in one section of beam
5	Hundreds of floaters in one section of beam
6	Innumerable floaters in one section of beam

values magnification × 16 height of slit in position 2 width of slit in position 10 (Kristensen 1968)

The grade of chamber angle pigmentation was studied carefully in every eye of the material in connection with gonioscopy

The pigmentation in the chamber angle was graded I–IV according to Tarkkanen (1962) Grade I *No pigment at all or only a few pigment granules on Schwalbe s line in the lower quadrants of the angle* Grade II Schwalbe s line pigmented all around the angle with some pigmentation of the posterior trabeculae in the lower quadrants Grade III Schwalbe s line more heavily pigmented around the angle as well as the posterior trabeculae in the lower quadrants The posterior trabeculae in the upper quadrants only lightly pigmented Grade IV A very heavy pigmentation of the entire angle in all quadrants Often thick masses of pigment seen on the trabeculae

The clinical and statistical correlations between the chamber angle pigmentation grade the degree of pigment liberation and the elevation of IOP during CPT in both eyes with and without pseudoexfoliation were determined.

Statistical analysis of the results was performed with the chi square tests and non parametrical methods using te Kolmogorov Smirnov two sample test and Spearman s correlation coefficient

Results

Pigment was liberated in the aqueous during CPT in 88 (31 9 %) of the 276 eyes (Table II) Very profuse pigment liberation (Grade 6) was seen fairly seldom, in no more than six eyes IOP rose concomitantly and significantly ≧ 8 mmHg in five of these eyes two with capsular glaucoma two with pigmentary glaucoma and in one eye after contusion of the globe The greatest IOP elevations in the responders of the total series occurred in just these eyes

Table II

Degree of pigment liberation in aqueous humour during the cyclopentolate provocative test (Mitsui value) and correlation with the concomitant change in IOP in 276 eyes with suspected or untreated open angle glaucoma

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Borderline (rise of IOP = 5–7 mmHg)	18	4	2	2	0	2	0	28	0.86
Responders (rise of IOP ≧ 8 mmHg)	5	1	1	2	0	1	5	15	2.93
No of eyes	188	40	8	17	6	11	6	276	0.80
%	68.1	14.5	2.9	6.1	2.2	4.0	2.2	100.0	

Chi square test
(χ^2 = 12.56)

* The difference is significant at $P < 0.01$

Table III

Degree of pigment liberation in aqueous humour (Mitsui value) during the cyclopentolate provocative test in 276 eyes with or without pseudoexfoliation

	Without pseudo exfoliation	With pseudoexfoliation			
		+	++	+++	Total
Mean Mitsui value	0.58	1.38	1.70	2.33	1.[illegible]1*
(± SD)	(± 1.38)				(± 1.[illegible])
No of eyes	221	16	30	9	55

Kolmogorov–Smirnov two sample test D = 0.44[illegible]
* The difference is significant at $P < 0.001$

Table IV

Degree of pigment liberation in aqueous humour (Mitsui value) during the cyclopentolate provocative test and the grade of pigmentation in the chamber angle in 276 eyes

	Grade of pigmentation of the angle				
	I	II	III	IV	Total
Mean Mitsui value	0 25	0 69	1 41	3 44	0 80
No of eyes	59	162	46	9	276

Spearman s correlation coefficient $r = 0\ 36$ $P < 0\ 001$

Table V

Grade of pigmentation of the chamber angle and correlation with the result of the cyclopentolate provocative test (CPT) in 196 eyes with open angle glaucoma

Result of the CPT	Grade of pigmentation in the chamber angle					No
	I	II	III	IV	Mean (± SD)	
Non responders (rise of IOP $\leq$ 4 mmHg)	45	68	31	3	1 95* (± 0 58)	147
Borderline (rise of IOP = 5–7 mmHg)	4	15	8	3	2 33 (± 0 69)	30
Responders (rise of IOP $\geq$ 8 mmHg)	1	10	5	3	2 53* (± 0 72)	19
No of eyes	50	93	44	9	2 06 (± 0 60)	196

The difference is significant at $P < 0\ 001$

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Degree of pigment liberation in aqueous humour during the cyclopentolate provocative test (Mitsui value) and correlation with the concomitant change in IOP in 276 eyes with suspected or untreated open angle glaucoma

Result of the CPT	Degree of pigment liberation							No of eyes	Mean Mitsui value
	0	1	2	3	4	5	6		
Non responders (rise of IOP ≤ 4 mmHg)	165	35	5	13	6	8	1	233	0.66
Borderline (rise of IOP = 5–7 mmHg)	18	4	2	2	0	2	0	28	0.86
Responders (rise of IOP > 8 mmHg)	5	1	1	2	0	1	5	15	1.93*
No of eyes	188	40	8	17	6	11	6	276	0.80
%	68.1	14.5	2.9	6.1	2.2	4.0	2.2	100.0	

Chi square test (χ^2 = [illegible]) The difference is significant at $P < 0.01$

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Degree of pigment liberation in aqueous humour (Mitsui value) during the cyclopentolate provocative test and the grade of pigmentation in the chamber angle in 276 eyes

	Grade of pigmentation of the angle				
	I	II	III	IV	Total
Mean Mitsui value	0.[illegible]5	0.69	1.41	3.44	0.80
No of eyes	59	162	46	9	[illegible]6

Spearman's correlation coefficient $r = 0.36$ $P < 0.001$

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Grade of pigmentation of the chamber angle and correlation with the result of the cyclopentolate provocative test (CPT) in 196 eyes with open angle glaucoma

Result of the CPT	Grade of pigmentation in the chamber angle					No
	I	II	III	IV	Mean (± SD)	
Non responders (rise of IOP $\leq$ 4 mmHg)	45	68	31	3	1.95* (± 0.58)	147
Borderline (rise of IOP = 5–7 mmHg)	4	15	8	3	[illegible].33 (± 0.69)	30
Responders (rise of IOP $\geq$ 8 mmHg)	1	10	5	3	[illegible].53* (± 0.[illegible]2)	19
No of eyes	50	93	44	9	[illegible].06 (± 0.60)	196

The difference is significant at $P < 0.001$

(20 19 and 16 mmHg) The elevation of IOP was at its maximum 1–4 hours after the beginning of CPT and liberation of pigment in the aqueous humour was concurrently also most profuse The increase in IOP was always harmless and subsided within 4–6 hours

There was a statistically significant correlation ($P < 0.01$) between pigment liberation and elevation of IOP during CPT (Table II)

Eyes with pseudoexfoliation displayed a statistically highly significantly greater degree ($P < 0.001$) of pigment liberation in the aqueous during CPT than eyes without pseudoexfoliation (Table III)

A statistically highly significant correlation ($P < 0.001$) was likewise established between the grade of chamber angle pigmentation and degree of pigment liberation during CPT (Table IV)

The role of pigment in IOP elevations is apparent also from Table V A significant correlation was established between the grade of chamber angle pigmentation and the result of the cyclopentolate provocative test Pigmentation of the chamber angles was statistically highly significantly ($P < 0.001$) more pronounced in the responder than in the non responder eyes

Discussion

A positive response with IOP rising ≥ 8 mmHg during CPT was obtained in 21 of the total of 431 eyes in the material (Table III Part I Valle 1976) The responders included two eyes with pigmentary glaucoma one eye with open angle glaucoma in an elderly strongly myopic patient and one eye with suspected open angle glaucoma following contusion of the globe (Nos 1 2 3 4 in Table VIII Part II Valle 1976) There was very profuse pigment in the chamber angle of all these eyes Taking the 10 eyes with pseudoexfoliation into consideration 14 of the 21 responder eyes – two thirds – showed profuse or very profuse pigmentation of the trabecular meshwork It is known that exceptionally heavy pigment is often encountered chiefly because of degeneration of the pigment epithelium of the iris in the chamber angle and elsewhere in the anterior parts of eyes with pseudoexfoliation (e g Dvorak Theobald 1954 Petersen 1958 Tarkkanen 1962 Sugar 1966 Horven & Hutchinson 1967 Krause et al 1973) in eyes with pigmentary glaucoma (e g Sugar & Barbour 1949 Calhoun 1953 Bick 1957 Perkins & Jay 1960) in post contusion eyes (Tonjum 1968) and also in elderly subjects in association with malignant myopia (Duke Elder 1970)

In the present material a statistically highly significant correlation ($P < 0.001$) was demonstrated between the grade of chamber angle pigmenta

tion and pigment liberation (Table IV) The same observation without statistical analysis was reported by Mitsui & Takagi (1961) A statistically highly significant correlation ($P < 0\ 001$) was established also between the grade of chamber angle pigmentation and the cyclopentolate response (Table V) This is different from the finding reported by Kristensen (1968) using sympathomimetics He observed no difference in the pigmentation of trabecular meshwork of responder and non responder eyes

Pigment was liberated in the aqueous during CPT in 31 9 % (Table II) This is a higher frequency than the figure reported by Mitsui & Takagi (1961) for persons healthy in regard to glaucoma but distinctly lower than the frequency obtained in other earlier studies using sympathomimetics (Kristensen 1965 1968 Haddad et al 1970) or sympathomimetics and parasympatholytics as the mydriatic agent (Krause et al 1973) Mitsui & Takagi (1961) reported considerably less frequent and less profuse liberation of pigment with parasympatholytics than with 5 % phenylephrine This is understandable on theoretical grounds alone Consequently the results obtained in the pigment liberation test by sympathomimetics and parasympatholytics should not be compared as such because they are very different owing to the different pharmacologic effects of the drugs

Sympathomimetics are more suitable than parasympatholytics for the pigment liberation test since they cause more frequent and more profuse liberation of pigment (Mitsui & Takagi 1961) The effect on IOP is the reverse however Parasympatholytics have been found to provoke marked IOP elevations distinctly more frequently than sympathomimetics (Kronfeld et al 1943 Schimek & Lieberman 1961 Harris 1968) As these responses were the principal object of interest in the present investigation 1 % cyclopentolate a potent and fast acting parasympatholytic was selected as the drug to be used Administration of 1 % cyclopentolate fairly seldom produced very heavy pigment liberation (Grade 6) in the aqueous only in six eyes This observation concurs with the findings of Mitsui & Takagi (1961) after 1 % atropine and 1 % homatropine No other studies of pigment liberation with parasympatholytics alone have been reported in the literature

A statistically significant correlation ($P < 0\ 01$) was demonstrated between the liberation of pigment and elevation of IOP during CPT (Table II) This was accentuated in the extreme cases In connection with very heavy pigment liberation (Grade 6) considerable ad 20 mmHg concomitant IOP elevations were noted in most cases They reflected a manifest causal relationship between the heavy liberation of pigment in the aqueous and the elevation of IOP It is probable that very profusely liberated pigment may cause transient blocking of the trabecular meshwork inhibition or obstruction of aqueous outflow and

transient elevation of IOP as has been reported in some earlier studies (Mitsui & Takagi 1961 Kristensen 1965 1968 Aggarwal & Beveridge 1971) Experiments *in vivo* and *in vitro* with pigment suspension support this view (Petersen 1969)

It may be mentioned in this context that the author observed in connection with mydriasis caused by 1 % homatropine a 32 mmHg elevation of IOP in one and a 39 mmHg elevation in the other of two elderly patients of 70–80 years who both had severe open angle glaucoma without pseudoexfoliation and also a considerable cataract There was concurrent heavy pigment liberation (Grade 6) in the aqueous The chamber angles were open very heavily pigmented (Grades III and IV) As these patients had already been given miotic therapy earlier for several years they were unsuitable for inclusion in the present investigation series

Antecedent miotic therapy has been found to increase responses (Harris & Galin 1969) and liberation of pigment in old subjects (Kristensen 1968) The author is of the opinion that the very great IOP elevations which have been reported (Leydhecker 1954 Kristensen 1965 Harris 1968) and which occur sometimes in connection with mydriasis or cycloplegia in eyes with open angle glaucoma can be explained against this background No IOP increases above 70 mmHg were observed in the present series of eyes without antecedent therapy for glaucoma and when the chamber angles were open with certainty throughout

It appeared on the other hand although rarely that during CPT pigment was liberated very profusely in the aqueous without a concurrent rise in IOP (Table II) The same observation was made by Kristensen (1968) Why did the IOP not rise in these cases? The explanation is primarily the great individual variations in the aqueous dynamics Some eyes display during CPT a marked decrease in inflow (Valle 1974) and/or the reserves of aqueous outflow may be very great and then there is no elevation of IOP although outflow facility diminishes (Valle 1974)

Liberation of pigment during CPT was statistically highly significantly ($P < 0.001$) more profuse in eyes with pseudoexfoliation than in eyes without pseudoexfoliation (Table III) The same observation was made by Krause *et al.* (1973) Pigment liberation in the aqueous – though distinctly more infrequently and a smaller degree – was seen also in eyes without pseudoexfoliation Kristensen (1968) and Krause et al (1973) made the same observation whereas Tarkkanen (1962) established the reverse

Responses to CPT without any simultaneous liberation of pigment in the aqueous were also observed (Table II) This is different from Kristensen's (1968) observation using sympathomimetics he saw no IOP elevations in excess of 6 mmHg without a concurrent excessive pigment liberation

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FLUORESCEIN LABELLED DEXTRANS AS TRACER SUBSTANCE FOR EXPERIMENTAL ANGIOGRAPHS

Short Communication

BY

G CHIORALIA L. SALMINEN* H BAURMANN and F KREMER

Key words fluorescent dextrans – molecular weight – angiogram – rat eye

For angiographical procedures 20 normal pigmented and albino rats of about 900 g body weight were anaesthetized and fixed on a special rat holder (Sasaki et al 1976) The angiograms were recorded with a Topcon fundus camera TRC F3 on Tri X 27 DIN Kodak film after intravenous administration of 2[illegible] fluorescein labelled dextran (FD) 3 40 70 and 150 (molecular weight 3[illegible] 40 000 70 000 and 150 000 respectively) in a dose of 0 1 ml/100 g body wei[illegible] After the injection of FD 3 the last weak fluorescence in the retinal [illegible] was observed at 15 min (Fig 1 a and b) A more prolonged fluores[illegible] the retinal vessels was obtained after FD 40 After the injection [illegible] (Fig 2 a and b) and 150 (Fig 3 a and b) a brilliant fluorescence [illegible] vessels was observed at 30 min and even longer No leakage f[illegible] vessels was evident after any injection

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Fig 1 a and b
The ang ogram pigmented rat eye 0 3 second and 15 min after iv FD 3

The penetrability of ocular blood vessels to intravenously administered dextrans of various molecular weight differs greatly as shown in histologic sections by Salminen et al (19 6) For in vivo permeability studies for instance of abnormal retinal vessels the fluorescent dextrans offer a method to elucidate mechanism of leakage Further studies are in progress

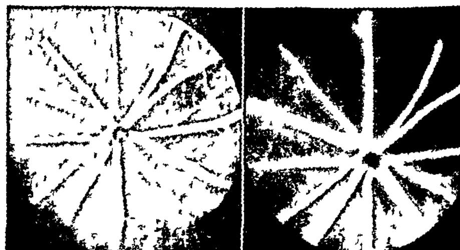


Fig 2 a and b
The angiogram of pigmented rat eye 0 3 second and 30 min after iv FD 40

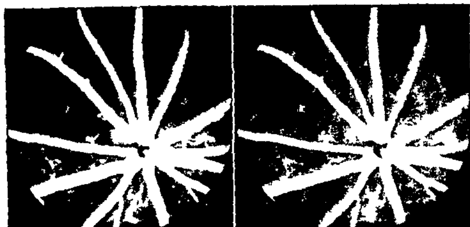


Fig 3 a and b
The angiogram of pigmented rat eye 15 min and 30 min after iv FD 150

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TRANSACTIONS OF THE *DANISH OPHTHALMOLOGICAL SOCIETY* 1974–1975

BY

ERIK SCHERFIG Secretary

460th Meeting September 28 1974 in Århus (Århus Municipal Hospital)

J Nehen *Spontaneous healing of retinoblastoma*

In a 52 year old man without a history of eye diseases or a familial predisposition to retinoblastoma an ophthalmological examination done because of presbyopia revealed a spontaneously healed retinoblastoma in an eye with normal visual acuity

The ophthalmoscopic appearances were characteristic

The possible causes why retinoblastomas *may regress were discussed*

Discussion *S Ry Andersen H Ehlers P Nellemann Sorensen*

I Hvidberg Hansen *Premedication for ophthalmic operations under local anaesthesia*

A study from the Eye Clinic of the Århus Municipal Hospital was submitted comparing the effect of two drugs used for premedication in two approximately equally large groups of patients 183 in all The drugs were dehydroben peridol and diazepam both administered im ½–1 h before the operation in an age dependent dose All patients *under 40 years of age were also given pethidine a quarter of an hour before the* operation

Diazepam was significantly better than dehydrobenzperidol according to an assessment of the condition before and during the operation Dehydrobenzperidol did not appear to have a sufficiently sedative or analgesic effect However neither drug seemed ideal

Discussion *K K Dreisler F Goldschmidt* and *Jens Edmund*

N Ehlers *? object inhibition in hemianopsia*

Has been published in The Proceedings of the First International Visual Field Symposium Marseilles 1974

Discussion *Viggo Dreyer Sv E Simonsen N Willumsen K K Dreisler* and *H Skydsgaard*

Ole Nissen and Rud Hoppe *Assessing aqueous drainage by means of acetazolamide An aid in diagnosing glaucoma*

Has been published in *Acta ophthal (Kbh)* 1975 53 537–553

Discussion *Sv E Simonsen* and *P Kjer*

H Ehlers *Panum s experiment once more*
(To be published later *in extenso*)

Instead of drawing the three vertical Panum lines (two for one eye and one for the other) on a sheet of white paper the lines were drawn on a piece of transparent cellophane At binocular fusion this gives a stereoscopic picture of only 2 lines sagittally displaced. Only now they are not seen in relation to the plane of the paper but far behind it Figures too can be fused in this way

The shiny light or haloes observed by Panum around the contours (identical with the halo in Helmholtz cross) is due to the white paper and disappears on the cellophane Objects anterior or posterior to the point of intersection of the visual lines show distinct suppressions at the sides of the median plane The paradox described by Bjerrum that lines which ought to be seen behind the paper instead of in front of it is easily explicable when the lines are viewed in the correct optical position in space and the white paper does not obstruct the view Suppression is a natural and necessary phenomenon in normal binocular vision A convincing illusion of fusion and stereoscopy may be created at various distances This explains why some squinters may have stereoscopic vision and it may cause erroneous interpretations in binocular instruments

The existence of suppressions is easily demonstrated by carrying both hands fingers spread horizontally towards each other while viewing a remote light surface through the space between the fingers When the finger tips pass the line of vision of the ipsilateral eye they fuse in the median plane and optical emptyness occurs at the sides

Discussion *N Willumsen*

T Sorensen and F Tageho j *Measurement of the flow of tears by 99 m technetium*

Preliminary report of a new method for determining lacrimation under basal conditions by radioactive technetium (Tc 99 m) in sterile physiological saline 10 μl of the solution are applied epiconjunctivally and the elimination is followed by a gamma camera and computer An initial rapid phase of about 5 min is followed by a slower phase which is estimated to represent the secretion and flow of tears under basal conditions Assuming that the volume of tears in the conjunctival sac is constant during this phase the secretion of tears may be calculated Preliminary investigations have shown a secretion of less than 1 μl/min

Discussion *K K Dreisler Sv Kessing* and *N Willumsen*

K Work *Fluorescein angiography and photocoagulation in senile macular degeneration*

The study comprises a total of 3[illegible] patients with senile macular degeneration

The aim was to differentiate by means of fluorescein angiography between so called vascular and avascular cases and to assess the result of treatment by photocoagulation

A total of 36 eyes were treated After a follow up period of 6 months 30 1% had improved visual acuity (i e reading at least 2 lines more on Snellen s chart) 50% were unchanged and 13 9% were worse (i e reading at least 2 lines less on the chart)

It was apparent also that the avascular cases responded appreciably better than the vascular ones This agrees with the experience of others

Lastly patients in whom the disease was of short duration i e less than 6 months have an essentially better *prognosis* than patients with a longer *duration* i e more than 12 months

Within the former group 60% of the treated cases showed improvement which was found in only 7 8% of the latter

On the basis of the findings *it is concluded* that patients with senile macular degeneration should be treated at an early stage and examined by means of fluorescein angiography with a view to differentiating between vascular and avascular cases

Discussion *H W Larsen Jens Edmund* and *K K Dreisler*

T Sørensen *Fiberoptics theory and applicability*

The theoretical basis of fiberoptics was briefly described A few of its industrial and medical applications were mentioned

General Meeting
September 28 1974 in Århus with Ernst Goldschmidt in the Chair

Reports were submitted from committees and commissions Moreover the General Meeting recommended the foundation of a contact lens *society* of ophthalmologists and opticians

461st Meeting November 30 1974 in Copenhagen
(Rigshospitalet)

Clinical pathological conference arranged by the University Institute of Ophthalmic Pathology
S Ky Andersen O A Jensen and H Fledelius

462nd Meeting February 15 1975 in Copenhagen
(Rigshospitalet)

Dyslexia Diagnosing and sorting

This part of the meeting was held together with school medical officers and school psychologists to arrive at closer collaboration for the benefit of dyslectic children

The subject was introduced by S Hesselholdt and H Skydsgaard Both established that in paedagogic as well as in ophthalmological quarters it was agreed that the ability for academic learning did not *depend upon the visual processes* provided that the visual acuity was at a reasonable level

H J Jensen mentioned various difficulties in examining slow readers i a the pre scriptions issued to the opticians and the limited time available in a busy general practice

Kjeld Mortensen recommended that a plan for examining dyslectic children be worked out by ophthalmologists and that all such children be referred for ophthal mological examination

Discussion *E Goldschmidt E Vesterdal Anders Poulsen* (school psychologist) *V Dreyer H J Jensen Zachau Christiansen* (representing the school medical officers) *T Posenberg E Skeller* and *O Hartkopp*

The school medical officers and the school psychologists also wished for a closer and possibly formalised collaboration concerning these children

J Fahmy *On the sterilisation of eye drops and ointments in the Eye Clinic of the Municipal Hospital Copenhagen*

To be published in Acta ophthal (Kbh)

No discussion

E Godtfredsen *Presuppositions and application of electrobiology also in neuro ophthalmology*

Recent decades advances in the physical chemical basic sciences have also benefited electrobiology New electrobiological methods and equipment have extended our know ledge of ocular structure and function and have improved diagnosis and treatment Keeping abreast in this development may be cumbersome and therefore it seems justified to sum up the present status from an interdisciplinary point of view this must even be well suited considering the well known common neuro ophthalmological spheres of interest On this motivation a brief account was given of the presuppositions and application of electrobiology with some histological trimmings

A line was drawn through the 400 year history of ele trobiology The first ?00 years (1600–1800) were concerned with friction electricity ele trical machines static electri city and sparks hich did not lead very far But thereafter the introduction of current electricity gave real impetus to the evolution and through the 19th century the pro perties of electricity were gradually disclosed *En route* there occurred a fusion with magnetism (Ørsted) light (Maxwell) and heat, previously interpreted as separate forces of nature but now recognized as different manifestations of the components of the electromagnetic spectrum at varying steps of energy Around 1900 followed the sensational discoveries of X rays natural radioactivity and the electron as well as Planck s quantum theory Classical physics had to be exchanged with modern physics Bohr s atom model new understanding of atomic and molecular reactions the structure of the periodic system etc In addition to the many theoretical novelties we were given practical methods for new investigation of biological tissues new insight into the interaction of excitable tissues with energy possibilities of converting energy into thermal ionizing or chemical activity The next step was to utilize this knowledge in our diagnostic and therapeutic armamentarium and here ophthalmology has been most favoured recently in fields such as laser and various types of scanning most recently EMI scanning

It was concluded that electrobiology and the intergrated photobiology including visual perception constitute an important and exciting field which concerns us all in different respects professionally in the field of extended ecology and not least on the personal level We are far more electrobiologically programmed than we think This applies right from exacting creative intellectual achievements to the activity of the minutest fibroblast in the effort to maintain its vital membrane potential Electro biology is a decisive factor in the modern profile of ophthalmology as a practised exact natural science

No discussion

Eilif Gregersen *Penalisation correspondence and squint angle*

In the literature it is generally agreed that penalisation can cure mild and moderate squint amblyopia but the agreement stops at the effect of penalisation upon abnormal retinal correspondence and squint angle Quéré (1972) and Pouliquen (197?) have reported that penalisation is able to normalise abnormal retinal correspondence but this could not be confirmed by Haase (1974)

Pouliquen (197?) and Réthy and Gal (1968) found a marked Haase (19 4) only a moderate reduction of the squint angle during penalisation However it should be mentioned that many patients of all three series were provided with stronger plus glasses during the penalisation as increased hypermetropia was disclosed in a large number of them in the course of the treatment

Our series comprises ?5 children with esotropia in whom conventional occlusion had been given up (in 22 cases because the patients felt it to be too much of a strain and in 3 cases because we felt it was ineffective) The 25 patients represent consecutive cases of occlusion therapy given up in a squint clientele of about ?00 new squinting children *per annum*

The mean age is ? years (range 3–8 years) and the squint had been recognized for an average of 4 years before penalisation was instituted The preceding ineffective occlusion therapy had been continued for an average of 8 months (range 1–?3 months) Mean refraction +3 0 (range from +1 0 to +7 0)

The penalisation had a marked effect upon the amblyopia (Gregersen Pontoppidan & Rindziunski 1974)

Correspondence was studied by synoptophore and Aulhorn s phase difference haploscope Prior to penalisation normal retinal correspondence was found in 2 patients while it was unknown i e unassessable in 13 and abnormal in 10 The correspondence altered from abnormal to normal in only one patient whose squint angle was reduced to ? in the course of penalisation

The mean deviation in the material did not exhibit any significant difference before and after penalisation In this connection it must be emphasised that we recorded only changes in deviation which occurred with unchanged glass correction (The mean deviation was ?? prism dioptres before and 1? after penalisation)

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Pouliquen P (197?) *Klin Mbl Augenheilk 161* 130–139
Quere M A (1972) *Klin Mbl Augenheilk 161* 140–155
Rethy I & Gal Zs (1968) *Acta ophthal (Kbh) 46* 757–766

Discussion A *Norskov P Brændstrup O Hartkopp* and *H J Jensen*

Gudrun Voigt (guest) *Polarisation of light Demonstration of phenomena*

Approach Is the theory of a radial analyser in the fovea valid?

Formulation of problems Do entoptic phenomena of interference occur when light having one or several directions of polarisation at the same time is made to hit the fovea by means of special filters? If so what are the orientation shape colour duration movement/non movement of these phenomena?

The li ht around us consists of a mixture of unpolarised and of specially reflected linearly polarised light Therefore, it is of interest to study the relation of the eye to polarised light We know the yellow Haidinger brush which appears as an entoptic phenomenon and renders it possible to distinguish the polarisation direction of filters

The polarised light of the surroundings may be demonstrated by a rotating linearly polarised filter creating flickering interference phenomena

There are radial analysers with the direction of polarisation (I) radially varying (II) varying at right angles to the radius (III) varying periodically and in different ways

Hallden has advanced the theory that a sky compass consisting of a radial analyser I and double refractive material may explain the phenomenon Haidinger s brush

My preliminary findings (1) The theory of a sky compass functioning in the fovea can be rejected because this creates a green and purple spot with dextrorotatory and sinistrorotatory polarised light respectively while a Haidinger brush is visible (2) Haidinger s brush is seen monocularly in circularly polarised light in a way different from that reported by Shurcliff this is described in more detail (3) A delicate flicker is seen monocularly on consideration of a filter composed like III Rotation of the filter gives rise to interference figures Adaptation conditions must be accurately re corded and included in the interpretation of the findings

Optical information is gained from spatial and time variations in one or more of the parameters relating to the undulant nature of light Visualisation requires conver sion to amplitude and frequency This may be done by moire methods or the creation of polar coordinates

Just as light on reflection may be divided into two types linearly polarised light with the directions of polarisation at right angles to each other fluid crystals divide light into dextrorotatory and sinistrorotatory polarised light one type is reflected and the other is absorbed

Polarised light has biological and phytophysiological effects by which bees and ants can orient themselves Its practical application is increasing Therefore ophthalmo logists must have some knowledge of its function and effect Progress can be made only through interdisciplinary collaboration.

Reference was made to Poul Klee s book The Thinking Eye by demonstrating Klee s ballet dancer made of polaroid material by the author

Discussion V *Dreyer* and *E Godtfredsen*

M S Norn *Immunoglobulin and ESR in endogenous uveitis*

In a study of 300 consecutive patients with endogenous uveitis by the quantitative immunochemical electrophoretic rocket method of Laurell the IgG was found to be elevated in 24%, IgA in 17% and IgM in 10%.

The immunoglobulins were most often elevated in binocular cases (47% as compared with 35% in monocular cases $P < 0.05$) and in anterior uveitis (44% against 24% in posterior uveitis $P < 0.01$)

ESR was elevated in 45% most often in acute fibrinous iritis (70%) most rarely in posterior uveitis (16%)

Published in Brit J Ophthal 1976 *60* 299–301

No discussion

Postgraduate Course May 2–4 1975 at Scanticon Århus

Subject Neuro ophthalmology The course was arranged by Th Rosenberg and the teachers were Paul Enoksson Lars Frisén Hans Bynke Nils Gunnar Henriksson Åke Kjallquist Jan Brismar and Christiana Raitta

463rd Meeting May 3 1975 at Scanticon Århus

Bjerrum Memorial Lecture Professor Rudolf Klotı *Iridectomy*

The Victor Larsen Foundation Hans Fledelius was awarded a grant for his studies on the visual development in children born prematurely (Published in *Acta ophthal (Kbh) Suppl 125* 1976)

JUDICIA DE NOVIS LIBRIS

Rahi A H S & Garner A Immunopathology of the eye Blackwell Scientific Publications Oxford London Edinburgh Melbourne 1976 343 pages price £ 11.5

The authors are general pathologists attached to the Institute of Ophthalmology London that Mekka for eye pathology from which so many excellent papers have issued during many years

The book is unusually well disposed and well written The first three chapters deal with basic immune mechanisms under normal and pathological conditions and with the concepts of autoimmune disease Not least the last chapter mentioned is evidence of the critical faculty of the authors

The following 8 chapters deal with immunological processes in the eye and its surroundings In the very important last chapters immunology of ocular tumours and ocular involvement in systemic immune disorders are dealt with Many diagrammes make the immunological mechanisms more easily understandable for the reader The literature is up to date but as so often in English works other main languages are not given a quite fair deal

The eye with its many well defined structures so often apt to immunological disorders is an ideal subject for study of this kind This book written by two experienced immunologists will be of great interest for all experimental or clinical working immunologists as well as for all ophthalmologists and it is highly recommended

S Ry Andersen

Larsen Hans Walther The Ocular Fundus A Colour Atlas Munksgaard & W B Saunders Copenhagen, Philadelphia London Toronto 1976 pp 195 (Dkr 200)

This new book can be considered as a concise revised edition of the author s well known book Manual and Colour Atlas of the Ocular Fundus of the Eye (1969)

The book contains 523 colour photographs which are identical with those of the manual They cover the majority of important ophthalmoscopical findings including both normal findings and those found in systemic and eye diseases There are no fluorescein angiography special filter or infrared photographs The photographs are well chosen Several series of photographs taken at monthly intervals follow the development in the same patient The corresponding slides may be effectively used in teaching students

The text has not been changed from the Manual it gives a concise and comprehensive description of the subject the ophthalmoscopical findings differential diagnosis and histology In order to condense the edition the detailed case histories and references from the Manual have not been included Instead the photographs have concise and comprehensive new texts which facilitate the reading of the book

The author has wished to produce a good and reasonably priced textbook concerning ophthalmoscopical findings In this he has succeeded extremely well The relevant sections of the Manual have been selected making an attractive and handy book that is easy to use A classic – which is strongly recommended to all trainee ophthalmologists and one which should be found in every eye department

M S Norn

VARIA

Neuro Ophthalmology Course

will take place January 4-6 1977 in Doral Beach Hotel Miami Beach Florida. The annual Neuro Ophthalmology Course will emphasize the following topics Cerebro vascular Disease Computerized Axial Tomography in Neuro Ophthalmology Anatomy and Diseases of the Parasellar Area Clinical case material will be presented for general discussion and question and answer sessions will include audience participation Registrants are invited to submit short free papers on clinical subjects (by November 19 6)

For further informations Contact Gaby Kressly adm assistent University of Miami School of Medicine P O Box 5708 ? Florida 33152

Medical and Surgical Complications of Uveitis

A postgraduate course in *Medical and Surgical Complications of Uveitis* will be arranged at Cole Hall San Francisco on December 2-3 1976 For information please write Extended Programs in Medical Education University of California 569 U San Francisco California 94143 or call (415) 666-4?51

The Fourth International Medical Contact Lens Symposium

will be held May 9th-10th 19 8 in the International Conference Hall Kyoto Japan. The official language is English The symposium will feature opening and closing ceremonies special lectures symposia and a technical exhibition For further informations contact Hikaru Hamano M D secretary general Kyoto International Conference Hall Takaraike Sakyoku Kyoto 606 Japan Telex 5422-353

XI Congreso Argentino de Oftalmologia

will be held from 2nd through 8th of November 1979 in the city of Mar del Plata. Contact dr Hugo D Nano Casilla de Correo 136? 600 Mar del Plata Argentina

I II International Course of Ophthalmology of the Instituto Barraquer

will be held from May 15 to 20 19 7 in Barcelona The topics are lens glaucoma, strabism cornea retina vitreous optic nerve and miscellanea There will be televised surgical session film session basic courses and scientific sessions The official languages are English French and Spanish For further information contact Instituto Barraquer Laforja 88 Barcelona (Spain

ACTA OPHTHALMOLOGICA VOL. 54 1976

Department of Ophthalmology
(Heads: P. Brændstrup, S. E. Lorentzen, M. S. Norn and K. Norskov)
and Department of Clinical Chemistry (Head: C. Brun)
Kommunehospitalet, Copenhagen

CONCENTRATIONS OF SOME RIBONUCLEOTIDES, L-LACTATE AND PYRUVATE IN HUMAN SENILE CATARACTOUS LENSES WITH SPECIAL REFERENCE TO ANTERIOR CAPSULAR/SUBCAPSULAR OPACITY

BY

A. BRUUN LAURSEN

The concentrations of some ribonucleoside tri- and diphosphates, adenosine-5'-monophosphate, L-lactate and pyruvate were determined in human senile cataractous lenses removed during cataract operations. Pyruvate concentrations were found to be negligible (median = 36 μmol/kg lens wet weight) in 15 human senile cataractous lenses.

On the basis of correlations between the biomicroscopic appearances of the senile cataractous lenses (N = 80) and the concentrations and ratios of the metabolites in question, the following classification was found to be justified:

1. Immature cataractous lenses without anterior capsular/subcapsular opacity: high levels of ribonucleoside triphosphates (RTP), high sums of RTP, ribonucleoside diphosphates (RDP) and adenosine-5'-monophosphate (AMP) as well as high levels of L-lactate and high ratios of L-lactate in the lens/L-lactate in the aqueous.

2. Immature cataractous lenses with anterior capsular/subcapsular opacity: intermediate levels of RTP, intermediate values for the sums of RTP, RDP and AMP, high L-lactate levels and intermediate values of the ratios of L-lactate in the lens/L-lactate in the aqueous.

3. Totally opaque lenses, which all had extensive anterior capsular/sub-

Received October 5, 1975.

capsular opacity low values for the concentrations of lens RTP for the sums of RTP RDP and AMP and for lens L lactate Low ratios of L lactate in the lens L lactate in the aqueous

Key words cataracts senile – opacity anterior capsular/subcapsular – ribonucleotides – L lactate – pyruvate

De Wecker (1886) made a survey of histopathological findings in cataracte capsulaire in human senile cataract This condition was stated to be associated with wrinkles of the lens capsule as well as degenerative changes and vacuolation in the epithelial layer Hess (1905) and Vogt (1914) described vacuoles at or just beneath the level of the anterior capsule of the lens on biomicroscopical examinations of human senile cataracts Since the literature seems to contain no information about the concentrations of metabolites in lenses with this particular type of opacity the present study paid special attention to a possible correlation between the biomicroscopical appearance of the anterior surface of the senile cataractous lenses and the concentrations of certain metabolites ribonucleoside triphosphates (RTP – see Methods) ribonucleoside diphosphates (RDP – see Methods) and adenosine 5 monophosphate (AMP) as well as pyruvate and L lactate L lactate was also determined in the aqueous humour so that the concentration ratio of L lactate in the lens/L lactate in the aqueous could be calculated

Material

The material of this study comprises 80 patients aged 55–93 years with senile cataracts The patients were fasted for about 10 h before the samples were taken Patients with additional eye disease diabetes mellitus or fasting blood sugar concentration > 6 1 mmol l were excluded Moreover patients treated with drugs of the digitalis group as well as patients treated with local or universal corticosteroid during the period of cataract development were excluded Lenses extracted extracapsularly and lenses treated with the proteolytic enzyme α chymotrypsin during the operative procedure were also excluded Mydriasis for the purposes of biomicroscopical cataract classification and per operative dilatation was produced by means of 0 5 % cyclopentolate The patients had retrobulbar anaesthesia (1 5–2 0 ml of 1 % carbocaine i e mepivacaini chloridum NFN without adrenaline or noradrenaline) The cataracts are classified in the legend Table III The extension and density of the cataract

were evaluated by slit lamp examination and ophthalmoscopy grade 1 lenses comprised immature cataractous lenses with slight extension of the opacities and a high degree of transparency grade 2 lenses comprised more heavily affected immature cataractous lenses grade 3 lenses were totally opaque

Methods

Aqueous humour was aspirated through a keratotomy just before the anterior chamber was opened The chamber was emptied of aqueous humour The aqueous was immediately heated to boiling point and then frozen on dry ice (Bruun Laursen & Lorentzen 1975) The lens was cryo extracted and while still attached to the tip of the cryo pencil rinsed with a few drops of 0 9 % saline The lens was cautiously wiped with fine gauze and then dropped into liquid nitrogen (-190 C) where it remained until homogenization took place The frozen lens was crushed in a steel block precooled in liquid nitrogen. The frozen lens powder was carefully mixed and by means of a steel spatula precooled in liquid nitrogen transferred to a 5 ml Potter Elvehjem homogenizer containing 1 00 ml of perchloric acid (0 6 mol/l) precooled at 4°C Homogenization at 100 r p m took place in ice bath for 2 min. The solution was placed in the refrigerator (4°C) for 30 min and then mixed. Centrifugation was performed at 3000 r p m for 10 min The supernatant was removed and titrated with a solution containing KOH (3 36 mol/l) - triethanolamine (TEA - 0 33 mol/l) to pH ca [illegible] $KClO_4$ precipitated at 0°C and was removed by centrifugation

The RTP RDP AMP pyruvate and L lactate concentrations of the lenses were determined by enzymatic spectrophotometrical procedures according to Biochemica Boehringer with certain modifications Readings of the absorbances of the assay systems were taken before and after the additions of enzymes Changes in absorbance were recorded at 340 nm in Helma 103 glass cuvettes with 10 mm light paths at room temperature by means of a Beckman DB spectrophotometer Aqua redestillata sterilisata was used. We added equivalent amounts of the same homogenate to the blank cuvette (to which no enzyme wa added) and the assay cuvette This was done in order to avoid a protracted unspecific rise in absorbance a phenomenon which was very frequently observed in the assay systems if water was added to the blank cuvette instead of homogenate This unspecific rise in absorbance may be due to photoactive pigments in the lenses (Cremer Bartels 1969) Corrections were made for possible unspecific changes in absorbance due to possible contaminations of the reagents with unwanted enzyme substrates This was done by recording the absorbance at 340 nm in an assay system where neutralized perchloric acid substituted lens homogenate

In RDP AMP determinations we had to add EDTA (91 mmol/l assay mixture) in order to prevent coarse flocculation after the addition of lens homogenate This flocculation was probably due to precipitation of Mg + of the assay mixture as phosphates Furthermore we added ATP (adenosine 5 triphosphate - 41 μmol/l assay mixture) in order to ensure that all AMP was determined since the myokinase activated conversion of AMP to ADP (adenosine 5 diphosphate) requires ATP Detailed descriptions of the procedures can be obtained on application to the author All determinations were duplicated

The accuracies of the enzymatic spectrophotometrical procedures appear in Table I Table II gives information on the reproducibilities of the methods (surgical procedures homogenization + deproteinization and enzymatic spectrophotometrical procedures) as well as on interindividual variations

According to Biochemica Boehringer the ribonucleoside triphosphate determinations include adenosine 5 guanosine 5 uridine 5 and inosine 5 triphosphates According to Biochemica Boehringer and Lowry & Passonneau (19 2) the ribonucleoside di phosphates determined are adenosine 5 diphosphate and at essentially lower rates guanosine 5 uridine 5 inosine 5 and cytidine 5 diphosphates AMP determination is not said to be unspecific

Accuracy and reproducibility for L lactate determinations in aqueous humour were investigated by Bruun Laursen & Lorentzen (1975) and by Bruun Laursen (19/5) Buffer pH 8 5 was used for the determinations of aqueous humour and lens L lactate concentrations

The figures were treated statistically by means of non parametric procedures medians 25 % and 75 % percentiles and ranges (numerical differences between the highest and lowest observations) Comparisons between different groups were carried out by means of the Wilcoxon test for two samples (the Mann Whitney test) and age concentration correlations were tested by means of the Spearman rank *correlation coefficient* These procedures have been described by e g Juul Therkelsen (1968) and Andersen (19 ?)

Table I

R covers experiments in pooled homogenates of human senile cataractous lenses. Individual lens homogenates were pooled One half of a pool was enriched with a solution containing substrate An equivalent amount of water was added to the other half of the same pool The difference in substrate concentration between these two pools was considered to be the recovery The concentrations are given per kg lens homogenate

Substrate	N	Added	Recovery median	Range
ATP	9	200 μmol	172 μmol	10 μmol
	11	100 μmol	94 μmol	6 μmol
	11	50 μmol	46 μmol	15 μmol
ADP	14	33 μmol	26 μmol	16 μmol
AMP	14	17 μmol	10 μmol	8 μmol
L lactate	4	1 5 mmol	1 4 mmol	0
	4	0 75 mmol	0 7 mmol	0
Pyruvate	10	33 μmol	32 μmol	5 μmol

ATP ADP and AMP adenosine 5 tri di and monophosphates respectively

Table II

Variations of concentrations and ratios of some metabolites in eyes with clear lenses from 7 fasting 4–6 month old pigs The lenses were removed under general anaesthesia The time which elapsed from the opening of the anterior chamber to the freezing of the lenses in liquid nitrogen varied from 5 to 12 min. Concentrations are given per kg lens wet weight The L lactate concentrations of the aqueous humour were calculated per kg aqueous

	Parameters						
	RTP	RDP	AMP	RTP + RDP + AMP	(RTP + 1/2 RDP) / (RTP + RDP + AMP)	L lactate	L lactate lens / L lactate aq
	μmol/kg					mmol/kg	
N =	12	12	12	12	12	12	5
Median	2458	600	107	3254	0 87	8 0	1 0
25th percentile	2 78	472	90	3061	0 85	7 7	
75th percentile	2678	417	1 4	3444	0 91	8.5	
Range	720	675	109	1004	0 12	1 5	0 8

RTP = ribonucleoside triphosphate RDP = ribonucleoside diphosphate AMP = adenosine 5 monophosphate See Methods Aq = aqueous humour

Results

In Table III the lenses are listed in groups in accordance with the biomicroscopical observations For each group the results of measurements of metabolite concentrations are given All lens metabolite concentrations refer to lens wet weight

It appears that the highest ribonucleoside triphosphate concentrations occurred in the groups of immature cataractous lenses without anterior capsular/subcapsular opacity This is clearly seen in group A Fig 1 (median = 1200 μmol/kg lens range = 1395 N = 33) Significantly lower RTP concentrations ($P < 0.01$) were found in immature cataractous lenses with anterior capsular/subcapsular opacity (group B Fig 1 median = 493 μmol/kg lens range = 966 N = 21) Totally opaque lenses contained still lower ($P < 0.01$) RTP levels (group C Fig 1 median 293 μmol/kg lens range = 541 N = 26) As for the total amounts of RTP + RDP + AMP a similar gradient was found The imma

Table III

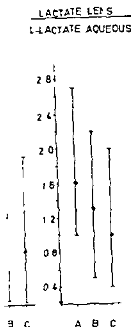
Some metabolite concentrations per kg lens wet weight in 80 human senile cataractous lenses

Cataract groups according to biomicroscopic findings 1 posterior subcapsular (posterior subcapsular tufaceous opacity) 2 posterior subcapsular + cortical (veil or spokelike anterior or posterior cortical opacities not affecting the lens capsule) 3 posterior subcapsular + nuclear (a nuclear opacities causing blurred insight to the posterior lens capsule b disciform opacity on transillumination of the dilated pupil) 4 posterior subcapsular anterior capsular/subcapsular opacity (whitish dots or irregular greyish coat apparently located in or just beneath the anterior lens capsule – see Fig 2) posterior subcapsular + cortical + nuclear totally opaque lenses (uniformly grey or brownish lenses with extensive anterior capsular/subcapsular opacity) 7 nuclear 8 cortical 9 immature cortical + nuclear 10 nuclear anterior capsular/subcapsular 11 immature cataracts with anterior capsular/subcapsular + posterior subcapsular + nuclear + cortical opacities 12 anterior capsular/subcapsular + posterior subcapsular + cortical 13 anterior capsular/subcapsular + cortical + nuclear

Abbreviations see Table II

	Cataract group	Age years	RTP (µmol/kg)	PDP (µmol/kg)	AMP (µmol/kg)	RTP + RDP + AMP (µmol/kg)	(RTP + 1/2 RDP) / (RTP + RDP + AMP)	L lactate in lens (mmol/kg)	L lactate lens / L lactate aqueous
	1	N =	7	7	7	7	7	7	6
Median		73	952	259	36	1172	0.85	8.1	1.7
25% percentile			618	154	9	915	0.80	7.0	1.3
75% percentile			1287	548	46	1814	0.89	11.5	2.8
Range		14	1075	563	126	1075	0.23	7.1	1.7
	2	N =	4	3	3	3	3	4	3
Median		80	132	183	97	1181	0.85	3.9	2.3
25% percentile			754					7.2	
75% percentile			1271					12.3	
Range		10	[illegible]	208	136	57	0.11	5.5	0.8

3	N = 6	1 1500	1 978	1 98	1 1936	0 88	8 4	1 0
4	N = 70	7	7	7	7	7	7	7
Median		491	219	0	730	0 82	0 7	1 3
25 % percentile		254	152	14	497	0 80	0 4	1 1
75 percentile		678	293	44	561	0 84	7 0	1 5
Range	83	623	177	70	784	0 91	8 6	1 7
[illegible]	[illegible]	[illegible]	1 [illegible]	1 [illegible]	1 [illegible]	1 0 [illegible]	2 [illegible] 2 0	1 1 [illegible]



f L lactate in lens/L lac
tous lenses
ular/subcapsular opacity

ular opacity See Fig 2

ntrations of the aqueous
nt the medians and the

nate AMP = adenosine
DP/RTP + RDP + AMP

ular opacity had a
ge was 1944 (group A
or capsular/subcapsular
B Fig 1 median = 134
values occurred ($P < 0.01$)
ig 1 median = 359 μmol/kg

Table III (cont.)

	Cataract group	Age years	RTP	RDP	AMP	RTP + RDP + AMP	RTP + 1/2 RDP / RTP + RDP + AMP	L lactate in lens	L lactate lens / L lactate aqueous
			µmol/kg					mmol/kg	
	9	N	4	4	1	4	4	4	3
Median		81	1186	402	57	1071	0.83	7.1	1.3
25% percentile			931	07	5	1385	0.82	6.5	
75% percentile			1498	477	132	2106	0.83	8.4	
Range		6	627	218	62	300	0.01	9.5	0.4
	10	N =	2	2	2	2	2	2	2
Median		70	500	117	22	638	0.80	6.1	1.3
Range		4	466	65	25	306	0.11	7.8	1.5
	11	N =	5	4	4	4	4	5	4
Median		68	624	226	30	876	0.84	4.8	0.9
25% percentile			438	78	[illegible]	442	0.80	4.1	0.8
75% percentile			1008	646	48	1752	0.88	8.2	1.1
Range		18	954	689	44	1687	0.10	6.7	0.4
	12	N =	6	6	6	6	6	6	6
Median		71	490	177	0	734	0.85	7.2	1.5
25% percentile			453	11	0	56	0.78	6.7	1.2
75% percentile			724	372	61	968	0.90	9.2	1.8
Range		7	304	330	109	[illegible]	0.14	3.9	1.0
	13	N =	1	1	1	1	1	1	1
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

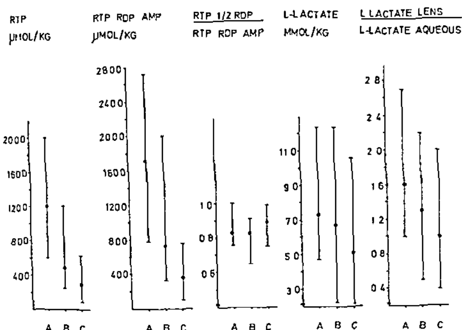


Fig 1

Distribution of some ribonucleotides L lactate and the ratios of L lactate in lens/L lactate in aqueous in 3 groups of human senile cataractous lenses

A Immature senile cataractous lenses without anterior capsular/subcapsular opacity (33 lenses)

B Immature cataractous lenses with anterior capsular/subcapsular opacity See Fig 2 (21 lenses)

C Totally opaque lenses (26 lenses)

The concentrations refer to lens wet weight The L lactate concentrations of the aqueous humour were expressed per kg aqueous The black dots represent the medians and the vertical lines represent the ranges

RTP = ribonucleotide triphosphate RDP = ribonucleotide diphosphate AMP = adenosine 5 monophosphate See Methods The ratio of RTP + 1/2 RDP/RTP + RDP + AMP represents the energy charge of the lens

ture cataractous lenses without anterior capsular/subcapsular opacity had a median value of 1718 μmol/kg lens for 31 lenses The range was 1944 (group A Fig 1) The immature cataractous lenses with anterior capsular/subcapsular opacity held lower ($P < 0\ 01$) total amounts (group B Fig 1 median = 734 μmol/kg lens range = 1687 N = 20) while still lower values occurred ($P < 0\ 01$) in the group of totally opaque lenses (group C Fig 1 median = 359 μmol/kg lens range = 662 N = 26)

The following observation indicates that the concentrations of the ribonucleotides are lower when anterior capsular/subcapsular opacity appears than when an isolated opacity of the posterior surface of the lens occurs 7 lenses with isolated posterior subcapsular cataract had higher values for RTP (median = 952 μmol kg lens) and for the total amounts of RTP + RDP + AMP (median - 1172 μmol kg lens) than had 7 immature cataractous lenses with both posterior subcapsular and anterior capsular/subcapsular opacity (medians = 491 and 730 μmol kg lens respectively 0 05 $> P >$ 0 02 in both cases

When lenses of the same degree of immaturity were compared it was found that the ribonucleotide levels were correlated to the biomicroscopical state of the anterior surface of the lens 26 lenses without anterior capsular/subcapsular opacity grade 1 (see Material) had a significantly higher ($P <$ 0 01) median RTP value (1237 μmol/kg lens) than had 7 immature cataractous lenses with anterior capsular subcapsular opacity grade 1 (median = 624 μmol/kg lens) As for the total amounts of RTP + RDP + AMP 24 immature grade 1 cataractous lenses without anterior capsular/subcapsular opacity (median = 1790 μmol kg

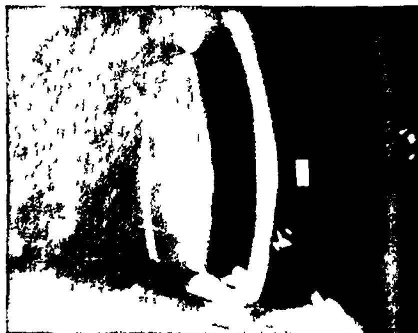


Fig 2

Anterior capsular subcapsular lens opacity (slit lamp photograph) The anterior surface of the lens appears to be wrinkled uneven and studded with white dots

lens) had higher (0 02 $> P >$ 0 01) values than had 7 immature grade 1 catarac tous lenses with this opacity (median = 961 μmol/kg) 79 % of the lenses without anterior capsular/subcapsular opacity were grade 1 while only 33 % of the lenses with this opacity were grade 1

As for the concentration ratio of RTP + 1/2 RDP/RTP + RDP + AMP which represents the energy charge of the lens no significant difference was found between immature cataractous lenses without (group A Fig 1 median = 0 83 range = 0 24 N = 31) and with (group B Fig 1 median = 0 83 range = 0 26 N = 20) anterior capsular/subcapsular opacity No decrease in this ratio was found in totally opaque lenses (group C Fig 1 median = 0 89 range = 0 24 N = 26) as compared with immature cataractous lenses with anterior capsular/subcapsular opacity On the contrary the ratios of totally opaque lenses were significantly higher ($P <$ 0 01) This may however be due to chance signifi cance since the difference between the medians of these two groups was very small

As for L lactate no significant difference was found between the concentrations of immature cataractous lenses without (group A Fig 1 median = 7 3 mmol/kg lens range = 7 7 N = 33) and with (group B Fig 1 median = 6 7 mmol/kg lens range = 10 2 N = 21) anterior capsular/subcapsular opacity Most groups in cluding the aggregate groups of immature cataractous lenses with and without anterior capsular/subcapsular opacity held significantly more L lactate than did the group of totally opaque lenses (group C Fig 1 median = 5 1 mmol/kg lens range = 8 5 N = 26) Only the group of pure nuclear cataract (median = 5 9 mmol/kg lens) and the group comprising immature cataractous lenses with anterior capsular/subcapsular opacity + posterior subcapsular + cortical + nuclear opacities (median = 4 8 mmol/kg lens) did not differ significantly from the group of totally opaque lenses as far as L lactate concentrations were concerned

The ratios of L lactate in the lens/L lactate in the aqueous were found to be higher (0 02 $> P >$ 0 01) in eyes with immature cataractous lenses without anterior capsular/subcapsular opacity (group A Fig 1 median = 1 6 range = 1 9 N = 28) than in eyes with immature cataractous lenses with anterior cap sular/subcapsular opacity (group B Fig 1 median = 1 3 range = 1 9 N = 20) Still lower values (0 05 $> P >$ 0 02) for this ratio were found in eyes with totally opaque lenses (group C Fig 1 median = 1 0 range = 1 6 N = 25)

Lenses with pure cortical cataract did not differ significantly from lenses with pure posterior subcapsular or nuclear cataract in any of the five parameters depicted graphically in Fig 1

Immature cataractous lenses without anterior capsular/subcapsular opacity were tested for possible correlations to age of the five parameters in question No such correlation was found

In the present study the median pyruvate concentration of 15 human immature and totally opaque senile cataractous lenses was 56 µmol/kg lens. The 25% and 75% percentiles were 26 and 87 µmol/kg respectively. The range was 148 µmol/kg lens. However the decreases in absorbance recorded were so small that these figures cannot be considered reliable.

No normal human lenses were available.

Discussion

These experiments point to a correlation between the ribonucleotide levels and the biomicroscopical condition of the anterior surface in human senile cataractous lenses. This observation does not appear to have been reported before in the literature. Lenses with anterior capsular/subcapsular opacity in this study occupied an intermediate position between immature cataractous lenses without this type of opacity (higher ribonucleotide concentrations) and totally opaque lenses (lower ribonucleotide concentrations). However the energy charges (ratios RTP + 1/2 RDP/RTP + RDP + AMP) of the lenses were no lower in immature cataractous lenses with anterior capsular/subcapsular opacity and in totally opaque lenses than in immature cataractous lenses without anterior capsular/subcapsular opacity.

We were not able to locate the site(s) of the anterior capsular/subcapsular opacity precisely. However it does seem to be located close to the epithelium of the lens (Fig. [illegible]; de Wecker 1886) which in clear lenses forms a single layer of cells beneath the anterior lens capsule. ATP consuming cation transport of the lens is assumed to take place chiefly in the epithelium (Kinsey & Reddy [illegible]; Harris & Becker [illegible]). It is noteworthy that totally opaque lenses which have extensive anterior capsular/subcapsular opacity and low concentrations of ribonucleotides have been found to have higher water and sodium contents but lower potassium concentrations than have clear lenses and pure early cortical cataractous lenses (Maraini & Mangili 1973). In the present study immature cataractous lenses with anterior capsular/subcapsular opacity belonged mainly to the more opaque immature cataractous lenses. This may be due to a disturbance of the normal cation and water balance of these lenses. Anterior capsular/subcapsular opacity has not been seen in clear lenses of healthy eyes (Hess [illegible]; Vogt [illegible]; the author of the present study).

As far as the pure forms of nuclear, cortical, posterior subcapsular cataracts and totally opaque lenses are concerned the ribonucleotide concentrations of the present study are comparable with those found for the same groups by Maraini et al. (196[illegible]) for RTP and Friedburg (1972) for RTP and RDP.

Most of the ATP production of the lens is supposed to be derived from glycolysis Hockwin & Korte (1968) estimated that glycolysis accounted for 94 % of rabbit lens glucose consumption Hockwin et al (1971) estimated that 91 % of calf lens ATP was derived from the citric acid cycle Since the adenine nucleotides have been found to make up about two thirds of the ribonucleotides of human senile cataractous lenses (Maraini et al 1969 – concentrations referred to lens dry weight) and since ATP was found by the same authors to constitute two thirds of the ribonucleoside triphosphates it would be interesting to compare the ribonucleotide concentrations with the glycolytic activity of the cataractous lenses *in vivo* The ratio of lactate/pyruvate was found by Hohorst et al (1961) to represent the oxidation/reduction state of the cytoplasmatic nicotinamide dinucleotide in liver cells *in vivo* This ratio has been used as a parameter for glycolysis in the cornea (Reim & Lichte 1965 Reim et al 1968) and in the aqueous humour (Schutte et al 1972) However in the present study this ratio could not be determined precisely since the pyruvate concentrations of the lenses were found to be so low that they could not be determined with sufficient accuracy The figures obtained indicate however that the lens L lactate steady state concentrations are on an average 100–200 times higher than those of pyruvate This finding indicates a high rate of glycolysis in the cataractous lenses Wu & Racker (1959) estimated the glycolytic activity of Ehrlich ascites tumour cells which also have a high rate of glycolysis by means of one measurement of the lactate concentrations of the cells

In the present study the L lactate concentrations were statistically identical in immature cataractous lenses with and without anterior capsular/subcapsular opacity although there was a highly significant difference in the ribonucleotide concentrations of these groups However in totally opaque lenses low ribonucleotide levels and low L lactate levels did occur simultaneously

Murata & Okazawa (1972) found higher L lactate mean values per kg lens wet weight than we did 7 9 mmol/kg in 5 totally opaque 17 6 mmol/kg in 4 nuclear cataractous lenses As far as pyruvate is concerned these authors also found higher concentrations than we did (mean values ranging from 647 to 1114 μmol/kg) As far as can be determined these authors gave no details about the accuracies of their methods (Biochemica Boehringer) in their laboratory (written in Japanese) No further information has been found in the literature concerning pyruvate and lactate concentrations in human senile cataractous lenses *in vivo*

The ratio of L lactate in the lens/L lactate in the aqueous may give an impression of the balance between the lactate concentration in the water phase of the lens and the lactate concentration of the aqueous humour The average water percentages of the cataractous lenses in question probably range from

66 % to 77 % and the upper limit seems to be 88 % (Maraini & Mangili 1973) Therefore if the L lactate concentrations of the lens water and the aqueous humour were identical an average ratio between 0 66 and 0 77 would be expected and the maximal value for the ratio would be 0 88 The average value of the present material for the ratio was 1 0 in the group of lenses with the lowest ratios viz the group of totally opaque lenses (N = 25) In 3 cases the ratio was lower than 0 77 These findings indicate that even in totally opaque lenses there is a production of L lactate since the surplus of lactate in the lens water cannot be derived by diffusion from the aqueous humour

The variations within the individual groups of cataract are large in this material and in the few comparable materials in the literature as far as the parameters in question are concerned This is probably not due to technical errors only (see Tables I and II) One possible explanation might be an omission to quantify the extent of the opacification within the individual lenses E g one immature cataractous lens might have 10 % of its anterior surface affected by anterior capsular subcapsular opacity while another lens had 90 % of its anterior surface affected Both were classified as immature cataractous lenses with anterior capsular subcapsular opacity

On the basis of the information presented in this study it seems justifiable to distinguish between 3 types of human senile cataracts This distinction is founded on a correlation between biomicroscopical and biochemical findings

1 Immature cataractous lenses without anterior capsular/subcapsular opacity high levels of lens RTP RTP + RDP + AMP and L lactate High ratios of L lactate in the lens L lactate in the aqueous

2 Immature cataractous lenses with anterior capsular/subcapsular opacity intermediate lens RTP RTP + RDP + AMP High L-lactate concentrations Intermediate concentration ratios of L lactate in the lens/L lactate in the aqueous

3 Totally opaque lenses which all had extensive anterior capsular subcapsular opacity low values for lens RTP RTP + RDP + AMP L lactate and for the ratios of L lactate in the lens/L lactate in the aqueous Possibly high ratios of RTP + 1 2 RDP RTP + RDP + AMP (energy charge)

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EMBRYONAL SARCOMA OF THE ORBIT

A Clinical Review of 19 Danish Cases

BY

HANS FLEDELIUS

The present study deals with 19 Danish cases of embryonal sarcoma of the orbit. Eight patients are still alive however only six with long period survival (8–21 years)
The *contralateral* orbit (and eye) remained uninvolved in the 19 cases accordingly the six long period survivors all have normal social vision In 17 cases the *homolateral* eye was removed early or late in the clinical history Only one of the long period survivors has preserved the homolateral eye (and with useful vision 6/24 after surgery for irradiation cataract)
The nation wide investigation covers a period of 27 years It reflects the difficulties in diagnosing orbital tumours and the changes in therapeutic approach to date Megavoltage radiotherapy plus chemotherapy immediately after the initial biopsy is now considered the therapy of choice exenteration of the orbit is performed only in the case of a recurrence Against the background of the present and an earlier study centralization of Danish orbital malignancies in infants and children is advocated

Key words embryonal sarcoma of the orbit – rhabdomyosarcoma – orbital tumours in childhood – orbital malignancies – centralization – radiotherapy – chemotherapy – exenteration of the orbit

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Table I
Clinical features in 13 Danish cases of embryonal sarcoma of the orbit

Case No Initials	Sex Age (years)	Orbit involved tumour presentation in the orbit	Primary therapy S = surgical R = radiotherapy C = chemotherapy	Time interval of recurrence	Long term outcome
No 1 ES	male 16	right axial protrusion + upper nasal	S (biopsy) R S (exent.)		21 years survival
No 2 JJ	female 4	left axial protrusion	S (biopsy) R	40 days	dead after 8 months
No 3 CI	male	left upper part	S (extirp.)	14 months	dead after 2½ years
No 4 JRC	male 9	right upper nasal	S (biopsy) R	23 months	19 years survival
No 5 CIKA	female 11 1[illegible]	right axial protrusion upper part	S (exent.) R	2 months	dead after 6 months
No 6 NBH	female 1[illegible]	left lower nasal	S (extirp.)	6 months	dead after 6 years
No 7 IJ	female 10	left upper temporal	S (extirp.) R	5 months	dead after 14 months
No 8 HRC	female 13	right upper temporal axial protrusion	S (exent.)		17 years survival
No 9 PKI	male 1	left upper nasal + axial protrusion	S (extirp.)	13 months	dead after [illegible] years
No 10 DJ	female 1	right upper nasal	S (biopsy) R		15 years survival

(cont.)

Embryonal sarcoma (and/or rhabdomyosarcoma cf. discussion) is the most common primary orbital malignancy in childhood and early adolescence. A high mortality rate (50–75 %) makes this disease a continuous challenge as far as prompt diagnosis and optimum treatment are concerned.

Table I (cont.)

Case No Initials	Sex Age (years)	Orbit involved tumour presentation in the orbit	Primary therapy S = surgical R = radiotherapy C = chemotherapy	Time interval if recurrence	Long term outcome
No 11 KEM	male 7	right lower nasal	S (biopsy) R		9 years survival
No 12 JA	male 4	right axial protrusion + upper nasal	S (biopsy) R	4 months	dead after 6 months
No 13 TB	female 11	left upper temporal	S (biopsy) R		8 years survival
No 14 KL	male 1	right axial protrusion + upper nasal	S (biopsy) R	6 months	dead after 2 3/4 years
No 15 LEP	male 4	right axial protrusion + upper nasal	S (biopsy) R C	10 months	dead after 20 months
No 16 LE	female 4	left axial protrusion + lower nasal	S (biopsy) R	7 months	dead after 2 1/4 years
No 17 PCH	female 10	right axial protrusion + upper part	S (biopsy) R then S (exent.) C	7 months	dead after 11 months
No 18 SEN	female 3	right axial protrusion	S (biopsy) R	14 months	still alive after 1 1/ year
No 19 LD	female 1	right lower nasal	S (biopsy) R C		still alive after 9 months

The present study – an analysis of 19 Danish embryonal sarcoma cases over a 22 year period (1954–75) – is the first one to deal with the Danish experience concerning this serious orbital malignancy

4

Material and Methods

Collection of the sample Ten of the 19 cases were included in a recent Danish analysis of orbital tumours in infancy and childhood (Eldrup Jorgensen & Fledelius 1975) covering the first part of the period under study The remaining nine cases (since 1969) were either seen in the Ophthalmic Tumour Centre (of the Copenhagen University Eye Pathology Institute) or became known from inquiries at the radium centres neurosurgical departments and university eye clinics in Denmark At least some of these medical institutions are inevitably involved in cases of such seriousness The 19 cases of embryonal sarcoma of the orbit therefore probably represent the actual incidence in Denmark (population now 5 millions) during the 22 year period
Histopathology The Eye Pathology Institute was implicated in 16 of the 19 cases when orbital tissue was first removed for microscopical examination Specimens from all 19 cases were later re examined to confirm the diagnosis

Paraffin sections were stained routinely with haematoxylin eosin Some of the following special stains were also usually performed P A S Reticulin stain Alcian blue Masson trichrome Phosphotungstic acid haematoxylin

The initial biopsies were performed in various departments all over the country and tissue fixation was not always optimal For this reason among others embryonal sarcoma has been used as a collective term for the cases Cross striation of tumour cells is easily lost when fixation is not optimal and hours of searching are often required to demonstrate striation even in well fixed sections Moreover it may be difficult to decide whether the striation – when found – belongs to fragments of external eye muscles (a possibility which is suggested from some of the histological photos from the literature) or to true tumour cells Actually clear cut cross striation was not demonstrated in the specimens of the present series Another reason for using the collective term embryonal sarcoma is that the prognostic significance of a histopathological classification (according to degree of differentiation) has proved to be ambiguous (Ashton & Morgan 1965)

For reasons of differential diagnosis the urinary excretion levels of adrenaline and vanillylmandelic acid (VMA) were determined in the more recent part of the series (cases) All showed normal values except for a boy (case 14 Table I) with elevation prior to radiotherapy of a solitary orbital mass suggesting a chromaffin tumour (neuroblastoma) He was however included in the series because there was no evidence of (primary) tumours elsewhere and the tumour behaved exactly as an embryonal sarcoma clinically as well as histopathologically

Results

Over a period of 22 years (1954–75) 19 Danish cases of orbital embryonal sarcoma were registered representing about one case a year in Denmark The series is presented in Table I The case numbers 1–19 are referred to in the following

Age The age span was from 11 months to 16 years with a median age of 5 years 13 of the 19 were less than ten years old

Sex There were 8 boys and 11 girls (the difference is not statistically signi ficant) The mean age and the median age were a little lower for the girls than for the boys but this trend was statistically insignificant

Clinical data All tumours were *unilateral* – twelve on the right side and seven on the left side The *histories* were characteristically short In seven cases the period until surgery was only 2–3 weeks a further ten were verified within two months of the commencement of symptoms Only two had a longer history with ten and eighteen months respectively until biopsy or extirpation

In eight cases the tumour was primarily recognized as a mass in one of the eyelids (five in the upper lid and three in the lower lid) In two further cases protrusion of the eye was an additional feature In the remaining nine cases ocular protrusion was the predominant sign initially however only one of these nine showed isolated axial protrusion without evidence of palpebral in volvement

From the clinical records it could be estimated that the majority (80 per cent) of the tumours had their origin in the upper part of the orbit and only 20 per cent in the lower half With the orbit divided into quadrants the site of predilection (50 per cent of all cases) was the upper nasal quadrant None of the tumours first appeared in the lower temporal part of the orbit

Extirpation of tissue for microscopical examination took place in 10 different departments (ophthalmology 6 neurosurgery 2 surgery 1 and otorhinolaryngo logy 1) 12 patients had anterior orbitotomy In 7 patients a trans periosteal route was used (craniotomy in 5 a lateral approach in 2)

Primary therapy

Table I shows schematically the various *primary* therapeutic approaches during the sampling period Primary here indicates what was actually planned and carried out at the first manifestation of the orbital tumour i e before eventual recurrences necessitated new measures The division of Table I (into the first ten and the latter nine cases) refers to the date when megavoltage radiotherapy became available an event that greatly influenced the choice of therapy

a) *Surgery* was the main therapeutic measure in seven of the nineteen cases Two cases (Nos 5 8) were submitted to early exenteration of the orbit and four (Nos 3 6 7 9) had intended radical tumour extirpation (all however with recurrence at a later date) Exenteration of the orbit was further performed in one case (No 1) because of continued tumour growth in spite of the com mencement of conventional radiotherapy

or treated with kryothermy In two cases (Nos 16 17) more extensive excisions (including maxillectomy) were carried out but in vain

Only one of the thirteen recurrences was successfully treated In case No 4 exenteration of the orbit (scarcely two years after remission induced by irradiation) led to cure (19 years survival)

In the 11 lethal ca es of the series death was caused by tumour invasion of the intracranial contents

Therapy given in cases of survival Sequels to treatment

Table I shows that six patients have survived 8–21 years *Exenteration* of the orbit was the effective measure for three (Nos 1 4 8) They are all alive and well after 17–21 years their cosmetic blemish has been relieved by spectacle borne ectoprotheses

The last three cases were cured by *radiotherapy* In one case (No 10 a girl) of conventional radiotherapy the homolateral eyeball was enucleated prophylactically before irradiation to allow a high dosage She is now 15 years old (observation time 14 years) and is regarded as "pituitary insufficient (endocrine adiposity) She has however regularly menstruated since the age of thirteen The two remaining cases were given megavoltage therapy In one of them (No 13) the homolateral eye was later enucleated because of painful keratopathy regarded as a sequel to the radiotherapy (6000 rads given through one frontal field The other (No 11) developed cataract in the irradiated eye this was later operated upon and now has useful vision (6/24 with contact lens)

In all six cases the contralateral eye remained unaffected and with normal visual acuity The same is true of our last two cases (Nos 18 19) with only a hort observation period

So far post irradiation sarcoma has not occurred in the six patients with long period survival However one of them (No 8) received radiotherapy (radium tubes) in the early years of life for a facial haemangioma near the lower orbital margin on the side where embryonal sarcoma of the orbit occurred 11–12 years later Because of the very low dosage given (as is customary for haemangiomas in small infants if treated) this embryonal sarcoma was not considered a sequel to irradiation

Discussion

The *histopathological* designation Embryonal mesenchymal tumours and tumours of muscle comprises three varieties Embryonal sarcoma rhabdomyosarcoma and smooth muscle tumour (of which the last mentioned is extremely

rare in the orbit) The distinction between the two former types is based on the demonstration of cross striation of the tumour cells This however depends to a large extent upon the diligence with which they are sought (Harry 1975 in a recent review) a statement quoted from Ashton & Morgan (1965) Our own difficulties were briefly commented above in Material and Methods All 19 cases were without cross striation and accordingly designated embryonal sarcoma This was also the prevailing subtype (³/₄ of the total) in the largest orbital series ever published namely those of Porterfield & Zimmerman (1962) and of Jones et al (1966) with 55 and 62 cases respectively

Harry (1975) also gave a short recapitulation of the typical *clinical features* of the disease The usual male predominance has not been confirmed in the present series while age grouping accords with earlier series with about two thirds of the patients in the first decade of life We found – like Reese & Calhoun (1941) and Porterfield & Zimmerman (1962) – the upper nasal quadrant of the orbit to be involved more frequently than elsewhere but this was not confirmed by Ashton & Morgan (1965) or by Jones et al (1966) Admittedly it may be difficult in such rapidly progressing tumours to make a fair statement about the initial location of the mass

An initial excision of tumour tissue is necessary for diagnosis and the planning of therapy In some of the Danish (as well as foreign) cases the surgical entrance had been made through the orbital roof This transfrontal approach is still advocated by for instance Brihaye (1975) in cases where the localization of the lesion is not precisely known and where extensive exploration is recommended It is thus the preferred method when an optic nerve glioma is suspected of extending behind the optic foramen However when other orbital malignancies are suspected the transfrontal approach should be avoided (Jones et al 1966) The orbital periosteum should be kept intact by using an anterior approach (trans septal trans conjunctival) when possible The consequences of a breached periosteal barrier are evident limitations of radiotherapy and easier tumour invasion of the brain on recurrence (Wright 1974) In the present series 7 patients underwent primary trans periosteal surgery two of the *i* are among the long period survivors

For many years *surgery* (extenteration of the orbit) was the advocated treatment Porterfield & Zimmerman (1962) reported nine (out of 55) patients who were alive and well three or more years after exenteration but four of them had been treated by additional measures (radio and chemotherapy) Jones et al (1966) stressed from their sample (n = 62) that orbital exenteration cures about half of the cases of orbital rhabdomyosarcoma – provided that they were treated early in the course of the condition In their opinion surgery should be performed without delay that is without waiting for the eventual effect of

radiotherapy or chemotherapy This opinion has however been modified recently Reese s group now favours radiotherapy as the primary treatment (Reese 1970)

This shift to *radiotherapy* is based upon – among other factors – the continuous work of Lederman in London who since 1945 has persisted in his treatment (Lederman & Jones 1974) in spite of the strong statements above favouring primary surgery Megavoltage therapy (about 5000 rads over 5–7 weeks) is now given after confirmative biopsy In Lederman s series of 26 there are 12 with survival for more than five years five of the twelve had however required exenteration because of local recurrence (Lederman 1974) Recently Sagerman et al (1974) reported a series of 31 children from the USA Of the 21 alive two years after primary radiotherapy only three had exenteration performed because of recurrence The observation period is however short

Finally *chemotherapy* has entered the therapeutic scene The use of combined chemotherapy (together with surgery and radiotherapy) has been substantiated by Pratt et al (1972) and Heyn et al (1974) in series of childhood rhabdomyosarcomas numbering 20 and 84 patients respectively Although only 12 per cent (13/104) of the rhabdomyosarcomas were located in the orbits in general the positive experience also appears to be valid for the orbital rhabdomyosarcomas Moreover this location should be advantageous symptoms become evident early and the tumour is from the outset kept within an anatomically well defined area accessible to surgery and radiation

The above comments on treatment are based primarily upon some of the most important contributions from the literature The apparent inhomogeneity of the present data (and the small size of the series) prohibit too extensive conclusions The long period survivors (6/19) were treated in somewhat different ways It appears as if the aggressiveness of the tumour to some extent determines the outcome This was especially evident from some of the most recent fatal cases with apparently favourable conditions for therapy (early diagnosis all accepted therapeutics available)

From the present material a probably commonplace experience (not often mentioned in literature) may be advanced concerning the value of exophthalmometry in the diagnosis of recurrences after radiotherapy The initial remission usually leads to equal Hertel values or even to enophthalmus on the irradiated side Higher exophthalmometric values that occurred later were in all instances caused by orbital recurrence there were no late irradiation reactions or any of the other benign conditions so fervently hoped for A secondarily increased Hertel value therefore demands immediate exenteration Routine controls with ultrasonography also proved helpful in this context Tumour echopatterns were the first evidence of recurrence in two patients

In conclusion the present results are in fairly good accord with the knowledge derived from earlier embryonal sarcoma materials The obvious demands for immediate diagnosis and planning of therapy call for expertise from several medical specialities and centralisation of such serious malignancies of early age is considered highly desirable

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ORBITAL MALIGNANCIES IN INFANCY AND CHILDHOOD IN DENMARK

Recommendations for Diagnosis and Therapy

BY

HANS FLEDELIUS

Based on two clinical series concerning primary orbital tumours in Denmark (Eldrup Jorgensen & Fledelius 1975 Fledelius 1976) recommendations are given for diagnosis and therapy of orbital malignancies in infancy and childhood Centralization is strongly advocated

Key words orbital malignancies – paediatric age classes – centralization – radiotherapy – chemotherapy – orbital ultrasonography – orbital EMI scanning

The sporadical occurrence of orbital malignancies in childhood (Eldrup Jorgensen & Fledelius 1975) makes it difficult for the single department (ophthalmological paediatric neurosurgical or other) to establish a routine procedure concerning diagnosis and therapy

The low actual numbers however do not justify a minimizing of the problems connected with such patients After all the orbit is (according to Dargeon 1960) among the six most common sites of paediatric malignancies Further the diagnostic problems are intricate they demand optimum examining equipment to be employed skilfully and with the least possible delay Arguments for this

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view are evident from the preceding review dealing with the most frequent (and very rapidly expanding) early age tumour of the orbit embryonal sar coma and rhabdomyosarcoma (Fledelius 1976)

The tragic outcome of some recent Danish cases led to the establishment of a medical team covering several specialities (those mentioned on the top of the title page) Based on own experience as well as that of other tumour centres we have at present decided upon the following *recommendations* when orbital malignancies are suspected in Danish children Above all a *centrali ation* is considered important

The patients are admitted to the Paediatric Department TG of Rigshospitalet Copenhagen primarily to exclude underlying generalized disease (blood dys crasia, histiocytoses endocrine disturbance etc) The Paediatric Department works in close collaboration with the Danish Ophthalmic Tumour Centre (next door at Rigshospitalet) as well as the above mentioned team of specialists from the other relevant departments of the University Hospital and Radium Centre

A standardized examination scheme comprises primarily the atraumatic examinations (X ray + tomography EMI scanning orbital ultrasonography iso tope scanning) prior to traumatic procedures (carotid angiography orbito graphy orbital venography pneumo encephalography etc) which have often proven unnecessary and timewasting

After localization of the tumour an orbital biopsy is carried out Whenever possible an anterior approach is made in order to keep the periosteal barrier intact

If localized embryonal (or rhabdomyo) sarcoma is diagnosed megavoltage therapy is commenced immediately Chemotherapy (vincristine + dactinomycin cyclophosphamide) is given in conjunction with this and continued for at least 6 months Orbital exenteration (or even more extensive surgery) should only be performed if the tumour does not respond to treatment or at the first sign of recurrence

A recent case of embryonal sarcoma (which could have been included in the preceding Danish series as case No 20) was handled according to these recom mendations After a history of only 10 days the tumour was localized with EMI scanning and ultrasonography biopsy was performed by way of an ante rior orbitomy and combined irradiation/chemotherapy was started after a week

The long term outcome is still to be waited for in this single case In general however we hope that the scheduled approach will prove advantageous and fulfil our aims 1) A reduction of the mortality in cases of embryonal sarcoma as well as other orbital malignancies 2) a cosmetically and functionally accep table state for survivors i e preservation of the anatomical structures of the orbit and the visual acuity

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OCULAR HYPERTENSION

I. The Clinical Course During Ten Years Without Therapy. Aqueous Humour Dynamics

BY

ERIK LINNÉR

An initial group of 152 subjects with moderate ocular hypertension constituted the basic material of the present study. Antiglaucoma treatment was started in 8 men and in 6 women. A remaining group of 97 subjects were kept under clinical observation for ten years without antiglaucomatous therapy and without any evidence of progressive disc cupping or field defects. The intraocular pressure as well as the outflow facility showed a tendency to decrease with time, which was assumed to indicate a reduction in aqueous flow with increasing age. The tonographic findings support the view that the moderately elevated intraocular pressure is mainly due to an increased rate of aqueous flow.

Key words: aqueous flow – aqueous humour dynamics – borderline intraocular pressure – glaucoma differential diagnosis – intraocular pressure – long term follow up – ocular hypertension.

In trying to classify the level of intraocular pressure according to its clinical significance, efforts are made to define a borderline between pathologically elevated and normal pressures. From the clinical point of view it would be of

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great importance to define the significance of the level of intraocular pressure alone as a single parameter for making the diagnosis of early open angle glaucoma. A clinically meaningful figure for the upper limit of normal pressure cannot be exactly calculated by statistical means although the probability of glaucomatous lesions increases with increasing pressure. Friedenwald (1949) called that intraocular pressure which could be characterized as normal for one individual the normative value. This pressure is found to vary considerably but we are not able to determine its level clinically in the individual case. In the present study no attempt is made to differentiate between a high normative pressure and early glaucoma by using the term ocular hypertension in cases of moderately elevated intraocular pressure without glaucomatous lesions. The two diagnoses cannot be separated by using the pressure alone as a single parameter. The physician's responsibility to include all available information in his considerations remains and in uncertain cases he has to follow the clinical course over a long period of time. The purpose of this study was to examine a group of individuals with moderately elevated intraocular pressure. The clinical course during ten years without glaucomatherapy was followed. Previous results after one and three quarter years and after five years were reported together with Stromberg (Linnér & Stromberg 1964, 1966). Aqueous humour dynamics was analyzed.

Material

Group I consisted of 92 individuals with ocular hypertension observed for 10 years without glaucoma therapy. These individuals were detected by Stromberg in 1960 (Stromberg 1962) in a mass survey of the ocular tension at Skövde using Schiøtz tonometer. His study included a total number of 3789 men and 4[illegible]0 women aged 40 years or more.

The initial group considered to have a manifest ocular hypertension consisted of 15[illegible] individuals, i.e. about 2 % of the total population. The average pressure level was 5.6 scale readings with 7.5 g weight (25.8–21.9 mmHg according to the calibration table of Friedenwald 1957). In 1970, ten years after the beginning of this study, 134 subjects could be traced but only 92 individuals remained in the follow up group on whom complete data in 1970 could be obtained. They had been kept under a normal clinical observation but were not placed on any antiglaucomatous therapy. Only in cases where it was felt indicated was therapy started. This treated group included 8 men and 6 women. In certain of the patients' therapy had been started by other ophthal-

mologists on different indications and it was therefore not possible to evaluate these cases for the purpose of the present study

The group with ocular hypertension was examined in 1961–1962 1965 and 1970 The measurements were calculated for each eye separately The average age in 1970 was 66 years

Group II consisted of 451 individuals born between 1895 and 1905 They were taken from group II of 1965 initially consisting of 639 individuals at Skovde The initial ocular tension in 1960 was less than 21 mmHg The ocular tension was measured in 1961 and 1965 with the Schiotz tonometer In 1970 a hand held applanation tonometer according to Draeger was used All measurements were carried out with the subject in a recumbent position

Group III consisted of 90 individuals chosen at random from the list of case histories in the department of surgery at Skovde hospital There was no history of glaucoma They were born between 1896 and 1918 with an average age of 68 years

Methods

The intraocular pressure was measured in a recumbent position with a handheld applanation tonometer according to Draeger Tonographic examinations were performed with a standardized electronic Schiotz tonometer (Schwarzer Manufacturing Co Munich) The right eye was always examined before the left one Benoxinate 0 4 per cent (Novesin® Wander Berne) was used as topical anaesthetic. The P_0 and the facility of outflow in the first four minutes of the tracing were calculated by use of Friedenwald s tables of 1955 The ocular rigidity was determined from the measurements obtained by applanation and Schiotz tonometry as a ratio between log pressure difference and volume difference. The outflow facility was then corrected for ocular rigidity The rate of aqueous flow was calculated by use of applanation pressures and corrected outflow facility values assuming the episcleral venous pressure to be 10 mmHg

Ophthalmoscopic examinations were carried out The relationship between the horizontal diameters of the disc cupping and the optic disc cup/disc ratio was estimated In addition an index for the cup volume was approximated by using the square of the cup diameter times the depth of the cupping The estimation of the depth was limited to three steps The object was to use the results for comparative purposes only and no effort was made to obtain absolute figures

The central visual fields were examined on a tangent screen using an Autoplot apparatus

Results

The intraocular pressures measured by applanation in 19[illegible]0 are shown in Table I. Only a small difference was found between the mean values of group II and group III but group I shows a significantly higher level than these two groups.

Table I

The intraocular pressure (P_a) in the right eye of group I (ocular hypertension) group II (ocular normotension followed during 10 years) and group III (ocular normotension selected at random) as measured with applanation tonometry in recumbent position (mmHg) in 19[illegible]0

	Group		
	I	II	III
mean	[illegible]3 0	14 4	1[illegible] 3
SD	4 4	2 9	3 4
n	9[illegible]	4 1	87

n = number of subjects
SD = standard deviation

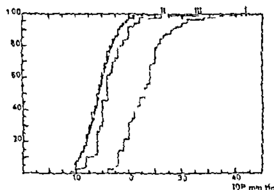


Fig. 1

The distribution of intraocular applanation pressure in the right eye of group I (ocular *hypertension*) *group* II (ocular normotension followed *during* 10 years) and group III (ocular normotension selected at random)

The distribution of the pressures in the three groups are demonstrated in Fig 1 Group I shows a positive skewness calculated to 1 35 and a positive excess calculated to 3 25

Group II is close to a normal Gaussian distribution with a positive skewness of 0 57 and a positive excess of 0 67

Group III deviates more than group II from a normal Gaussian distribution showing a positive skewness of 1 55 and a positive excess of 5 63

In group I with ocular hypertension the changes in intraocular pressure and in outflow facility during 10 years of observation are shown in Tables II and III Starting with the results in 1970 and calculating the differences during 5 and 10 years respectively there was a marked reduction in the number of cases A numerical reduction in P_0 and C with time was found throughout although comparisons including the results of 1970 only were significant The changes with time are demonstrated in Figs 2 and 3

Tables IV and V demonstrate the changes of intraocular pressure from 1961 to 1970 in group I and II The number of eyes in group I in which all measurements were available was only 22 and the differences were not significant In group II the changes during the time intervals 1960–1970 and 1965–1970

Table II

The change in intraocular pressure (P_0) and facility of aqueous outflow (C) in the right eye from 1961 to 1970 in group I (ocular hypertension) Starting from 92 right eyes in 1970 only those eyes are included where results were also recorded in 1965 and in 1961

Group		Year		
		1961	1965	1970
I	P_0 mean	25 0	23 8	22 8
	SD	3 7	3 6	4 1
	n	33	73	83
	C mean	0 24	0 23	0 20
	SD	0 088	0 082	0 076
	n	33	73	82

P = intraocular pressure measured with Schiotz tonometer (mmHg)
C = outflow facility (µl/min/mmHg)
SD = standard deviation
n = number of subjects

Table III

The differences at the various time intervals of the intraocular pressure (P_0) and outflow facility (C) obtained from Table II calculated by using Student's t test for pairing observations

Group I		Time interval		
		1965–1961	1970–1965	1970–1961
P	$\bar{D}$	−0 072	−1 256	−1 465
	SE	0 849	0 494	1 033
	n	27	68	26
		NS	$P < 0\ 01$	$P < 0\ 05$
C	$\bar{D}$	−0 003	−0 025	−0 034
	SE	0 014	0 010	0 014
	n	2	67	26
		NS	$P < 0\ 01$	$P < 0\ 05$

$\bar{D}$ = mean difference
SE = standard error of the mean
n = number of subjects
NS = no significance

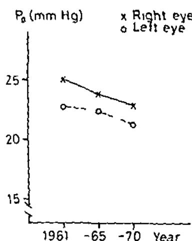


Fig 2

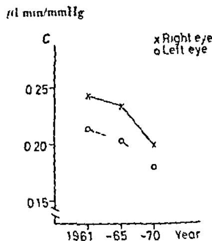


Fig 3

Fig 2 The change of the intraocular pressure in group I (ocular hypertension) during a 10 year period

Fig 3 The change of the outflow facility (mm³/min/mmHg) in group I (ocular hypertension) during a 10 year period

Table IV

The change in intraocular pressure of the right eye from 1961 to 1970 as measured with Schiotz tonometer (P_o) and applanation tonometer (P_a) respectively in group I (ocular hypertension) and in group II (ocular normotension)

Group		Year		
		P 1961	P_o 1965	1970
I n = 22	mean SE	25.3 0.84	24.8 0.88	P_o 23.6 0.81
II n = 451	mean SE	16.0 0.13	15.7 0.13	P_a 14.5 0.15

SE = standard error of the mean
n = number of subjects

Table V

The differences at the various time intervals of the intraocular pressure obtained from Table IV in group I (ocular hypertension) and group II (ocular normotension) All tests were made simultaneously using a profile analysis according to Morrison (1967)

Group		Time interval		
		1965–1961	1970–1965	1970–1961
I n = 22	$\overline{D}$ SE	−0.51 0.98 NS	−1.17 0.78 NS	−1.68 1.14 NS
II n = 451	$\overline{D}$ SE	−0.34 0.13 NS	−1.18 0.14 $P < 0.001$	−1.53 0.14 $P < 0.001$

n = number of subjects
$\overline{D}$ = mean difference
SE standard error of the mean
NS = no significance

Table VI

The change in estimated cup/disc ratio from 1965 to 1970 in group I (ocular hypertension). The differences were calculated by using Student's *t* test for pairing observations

		Cup/disc ratio		Difference 70-65
		1965	1970	
Right eye	mean	0.38	0.35	-0.02
	SE	0.018	0.020	0.014
	n	92	87	87
Left eye	mean	0.40	0.35	-0.055
	SE	0.017	0.022	0.015
	n	91	89	89

n number of subjects
SE standard error of the mean

were statistically significant. The reductions with time were numerically similar in group I and group II.

A falling tendency of both the intraocular pressure and of the outflow facility was recorded throughout the time intervals studied.

As shown in Table VI and Fig. 4 there was no evidence of an increasing

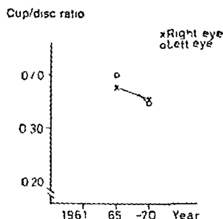


Fig. 4

The change of the cup/disc ratio in group I (ocular hypertension) during a 5 year period

Table VII

A comparison between the right eye of group I (ocular hypertension) and group III (ocular normotension selected at random in 19 0) The significance for differences between mean values were calculated simultaneously using a profile analysis according to Morrison (1967)

		Group I n = 71	Group III n = 86	Difference I-III
P_a	mean	2? 7	16 3	$P < 0\ 001$
	± SE	0 4?	0.34	
P_o	mean	22 4	16 2	$P < 0\ 001$
	± SE	0 43	0.32	
C	mean	0 20	0 27	$P < 0\ 01$
	± SE	0 009	0 009	
E	mean	0 0?1?	0 02?4	–
	± SE	0 0004	0 0004	
C_{rr}	mean	0 20	0 27	$P < 0\ 01$
	± SE	0 008	0 010	
F	mean	2 54	1 79	$P < 0\ 0$
	± SE	0 11	0 14	
Cup (vol)	mean	0 31	0 21	–
	± SE	0 047	0 03?	
Cup/disc ratio	mean	0 34	0 28	NS
	± SE	0 020	0 017	

P_a = intraocular pressure measured with applanation tonometer (mmHg)
P = intraocular pressure measured with Schiotz tonometer (mmHg)
C = facility of outflow (μl/min/mmHg)
E = ocular *rigidity coefficient*
C = facility of outflow (μl/min/mmHg) corrected for ocular rigidity
F – rate of aqueous flow (μl/min) calculated as F = C_{corr} (P_a – 10)
Cup (vol) = estimated volume of the cupping of the optic disc
Cup = estimated horizontal diameter of the cupping of the optic disc (cup/disc ratio)
SE = standard error of the mean
NS = no significance

Table VIII

The differences between right and left eyes in group I (ocular hypertension) and group III (ocular normotension selected at random in 19,0)

		Group I RE – LE	Group III RE – LE
P_a	mean ± SE	0 91 ± 0.57 n = 81 NS	0 40 ± 0 17 n = 90 $P < 0.05$
P_o	mean ± SE	1 48 ± 0 45 n = 71 $P < 0.01$	1 34 ± 0 19 n = 86 $P < 0.001$
C	mean ± SE	0 021 ± 0 007 n = 71 $P < 0.01$	0 027 ± 0 007 n = 85 $P < 0.001$
E	mean ± SE	0 001, ± 0 000 n = 71 $P < 0.001$	0 0022 ± 0 000 n = 84 $P < 0.001$
C_{cor}	mean ± SE	–0 0046 ± 0 008 n = 71 NS	–0 0013 ± 0 005 n = 84 NS
F	mean ± SE	0 069 ± 0 124 n = 71 NS	0 090 ± 0 0[illegible] n = 84 NS
Cup (vol)	mean ± SE	0 016 ± 0 036 n = [illegible] NS	–0 01[illegible] ± 0 01[illegible] n = 87 NS
Cup disc ratio	mean ± SE	0 018 ± 0 016 n = 75 NS	0 0045 ± 0 010 n = 88 NS

P_A = intraocular pressure measured with applanation tonometer (mmHg)
P_o = intraocular pressure measured with Schiotz tonometer (mmHg)
C = facility of outflow (µl min mmHg)
E = ocular rigidity coefficient
C_{cor} = facility of outflow (µl/min mmHg) corrected for ocular rigidity
F = rate of aqueous flow (µl min) calculated as $F = C_{cor} (P_a - 10)$
Cup (vol) = estimated volume of the cupping of the optic disc
Cup = estimated horizontal diameter of the cupping of the optic disc (cup/disc ratio)
SE = standard error of the mean
NS = no significance

cup/disc ratio from 1965 to 1970 There was no significant correlation between the estimated cup/disc ratio as well as the estimated cup volume and the initial level of the intraocular pressure in 1961 of group I

Examination of the visual fields using a tangent screen did not reveal any progressive field changes

The results for group I and group III and the differences between the mean values of the two groups are shown in Table VII A significant difference was found between the two groups concerning intraocular pressure outflow facility and rate of aqueous flow The average intraocular pressure was about 6 mmHg higher in group I than in group III and the average facility of outflow about 0 07 µl/min/mmHg lower The rate of aqueous flow was significantly higher in the group of eyes with ocular hypertension than in eyes with normal pressure There was a good agreement between the pressure values obtained by applanation and by Schiotz tonometer The ocular rigidity values were close to the average value 0 0215 and the values of outflow facility were therefore not significantly changed by correction for ocular rigidity

Correlation between age and ocular rigidity was calculated for group I and for group III No significant correlation was revealed

The estimated cup/disc ratio did not not show any significant differences between the two groups in spite of the presence of ocular hypertension for at least 10 years in group I

The differences between right and left eye are shown in Table VIII The applanation pressure values did not differ significantly The intraocular pressure value with Schiotz tonometer is taken from the beginning of the tonographic tracing It is common experience that the value in the second eye is lower than in the first one In this study the left eye was measured after the right eye and showed a lower pressure value The outflow facility was also higher in the first than in the second eye After correction for ocular rigidity the difference between right and left eye disappeared

There was no significant difference between right and left eye in the cup/disc ratio

Discussion

From the clinical point of view the following conclusion can be drawn a moderate ocular hypertension can be present for at least 10 years without a tendency toward further pressure elevation and in most cases without further clinical evidence of progressive disc cupping or visual field defects The clinical course is similar to that found in other longterm studies (Armaly 1969 Graham

1968 Leydhecker 1967 Norskov 1970 Perkins 1973) Thus there seems to exist individuals who can be characterized as having a high normative pressure

These observations might be of interest when one is trying to evaluate the importance of pressure levels as a single parameter for the diagnosis of early open angle glaucoma

There was found to be a consistent decreasing tendency with time of both the intraocular pressure and the outflow facility The number of observations are limited in some of these groups Although some of the differences are not significant it seems reasonable to believe that there is a general tendency towards decreasing intraocular pressure and outflow facility with increasing age In group I the overall decrease of the intraocular pressure can be estimated to be about 2 mmHg and the decrease of the outflow facility about 0 2 μl/min/mmHg Each of these two changes with time might indicate a reduction in the rate of aqueous flow This interpretation is made under the assumption that there is no other change of importance for the estimation of aqueous flow such as change of the episcleral venous pressure or other outflow pathways A mm decrease in the intraocular pressure without any other change corresponds to about 15 per cent flow reduction A simultaneous pressure reduction of 2 mmHg and facility reduction of 0 02 μl/min/mmHg corresponds to about 20–25 per cent reduction in flow

A reduction of 1 5 mmHg from 16 to 14 5 mmHg in group II corresponds to about 25 per cent reduction in outflow pressure and thus in aqueous flow assuming that there are no other changes during this period of 10 years In another study a reduction in aqueous flow in higher age groups was found in normal subject (Linnér 1959) Although these results are obtained in different subjects they indicate the same tendency toward a flow reduction with increasing age A decrease in outflow facility in higher age groups has also been reported (Johnson 1966 Lindholm et al 1965)

Physiological changes in the aqueous humour dynamics of the aging eye seems to be present both in individuals with moderate ocular hypertension and with ocular normotension

The method of tonography is impaired by reason of serious errors and uncertainties as pointed out by Linnér & Thorburn (1971) A method of tonography at constant pressure was therefore considered Thorburn (1973) used this method to estimate the facility of outflow in the right eye of subjects from three different groups One group consisted of young subjects Furthermore a number of 30 eyes were taken from group I with ocular hypertension in the present study Another 30 eyes were taken from group III with normotension also in the present study There was no significant difference neither between young and elderly subjects nor between elderly subjects with normotension and hyper

tension If one assumes that the constant pressure tonography gives a better estimate of the facility of outflow one would find a greater difference in the rate of aqueous flow between the normotensive and hypertensive group The flow rate difference would correspond to the difference in outflow pressure i e the flow rate in the hypertensive group is about twice as high as in the normo tensive group

Another factor which might be of some importance is the pseudofacility Goldmann (1968) reported a smaller pseudofacility in old than in young people It cannot be excluded that uveoscleral outflow and the episcleral venous pressure might have some influence although there is no evidence for such changes

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EFFECT OF THE LENGTH OF WEAR OF CONTACT LENSES ON CORNEAL SENSITIVITY

BY

MICHEL MILLODOT

Corneal touch thresholds (CTT) were determined once in the morning before inserting contact lenses then after 4 8 and 12 h of continuous wear Two groups of subjects participated in this study 1? persons wearing hard contact lenses and 15 wearing soft contact lenses All subjects were perfectly adapted to their contact lenses and had worn them for not less than three months It was found that hard contact lenses caused a progressive diminution of corneal sensitivity After 12 h corneal sensitivity was on average 110 % lower (that is an increase of the threshold) than in the morning Soft lenses also caused a progressive reduction of corneal sensitivity which after 12 h wear was on average 45 % lower than in the morning although there were marked differences Moreover 9 of the hard contact lens subjects had been tested a year earlier and it was found that their CTT after 8 h wear had slightly but not significantly diminished which indicated that these subjects had not adapted significantly to their lenses in one year

Key words hard contact lenses – soft contact lenses – corneal sensitivity – adaptation

The wear of contact lenses either hard or soft affects the corneal metabolism to some extent even if the lenses are well fitted and the patient perfectly adapted (e g Smelser 1952 Miller & Exford 1967 Mandell Polse & Fatt 1970 Farris Kubota & Mishima 1971 Bailey & Carney 1973) Along with this

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effect there is an infallible reduction of corneal sensitivity which has been noted by various authors (Boberg Ans 1955 Byron & Weseley 1961 Ko & Tomiyama 1963 Dixon 1964 Knoll & Williams 1970 Larke & Sabell 1971 Millodot 1974 Millodot 1975) However none of these studies has systematically evaluated the loss of sensitivity as a function of the number of hours wear of contact lenses In other words after 6 h wear for example is the loss of corneal sensitivity found to remain the same to worsen or to decrease with continued wear?

The purpose of this investigation is to provide systematic measurements of the diminution of corneal sensitivity as a function of the number of hours of wear of hard and soft contact lenses And also to assess how this effect is altered after one year of wear

Materials and Method

The Cochet Bonnet aesthesiometer (1960) based on the instrument devised by Boberg Ans (1955 1956) was used to stimulate the cornea The instrument consists of a monofilament of 0 12 mm diameter which can be extended to various lengths thereby producing pressures ranging from 11 to 200 mg/0 0113 mm The aesthesiometer was mounted in a holder allowing movement in x y and z axes by means of three knobs This set up makes it possible to obtain reliability in stimulating a corneal point and steady speed of application of the monofilament at right angles to the cornea (Fig 1) All measurements were taken when the humidity in the room did not exceed 60 % because the nylon monofilament is affected by humidity (Millodot & Larson 1967)

Two groups of subjects were tested The first group consisted of 12 subjects (7 females 5 males) between 21 and 31 years of age who wore hard contact lenses The second group consisted of 15 subjects (8 females 7 males) between 22 and 35 years of age who wore soft contact lenses All were successful contact lens wearers free of any complaints or any discernible eye pathology All had worn their lenses for no less than 3 months and the mean wearing time of these 27 subjects was 15 months (SD 9 2) These people had been fitted by various practitioners inside and outside the University and wore lenses from six different manufacturers

Each subject was asked to report in the morning prior to inserting his lenses and a measurement of the corneal touch threshold (CTT) of the left eye was made subjectively (Millodot 1973) stimulating a peripheral point (6 o clock) of the cornea This corneal point was chosen to avoid the apprehension effect provoked when stimulating the centre of the cornea (Bonnet & Millodot 1965)



Fig 1

A subject in place being tested for corneal sensitivity with the Cochet Bonnet aesthesiometer The subject is fixating a spot in front of him whilst the experimenter looks through the magnifying lens at the minimum bending of the nylon monofilament placed against the cornea

and because contact lenses affect the central as well as peripheral corneal sensitivity (Millodot 1975) The testing began with stimulation of the cornea with a low pressure and continued in an ascending fashion At each predetermined length (in increments of one half a cm) of the monofilament four to six contacts were made and the slightest bend of the nylon wire visible through a 4 3 magnifier was defined as corneal contact The subject was fixating an object on the opposite wall and he indicated when he felt the probe by pressing a bell From these readings the corneal touch thresholds was defined as the length of the monofilament for which the subject responded for 50 % of the number of stimulations This length was converted into pressure using a previously established calibration curve between length and pressure

The subjects were then asked to report to the laboratory after having worn their lenses continuously for 4 h CTT was assessed within one min of removal The subjects were again asked to report to the laboratory on another day after 8 h of continuous wear and finally an another day after 12 h of continuous wear CTT were also determined just after removal in these two instances

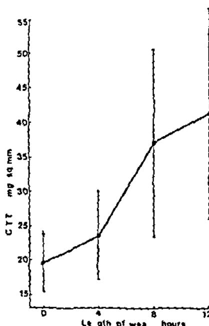


Fig 2

Relationship between the length of wear of hard contact lenses and peripheral corneal touch threshold (CTT) Each data point represents the mean of 12 subjects and the vertical lines represent ± 1 SD

Results

Effect of hard contact lenses

The corneal touch thresholds (CTT) obtained prior to insertion of the lenses and after 4 8 and 12 h of continuous wear are shown in Fig 2 The mean (and standard deviation) for the 12 subjects was found to be 19 63 mg/mm (4 19) prior to insertion After 4 h of wear CTT was slightly higher (23 6 mg/mm SD 6 53) but this value is nevertheless significantly different ($P < 0 01$) than in the morning After 8 h of continuous wear CTT was found to be markedly higher (that is sensitivity diminished) since it was equal to 37 04 mg/mm (13 65) which indicates a decrease of corneal of sensitivity of 89 % compared to its initial value in the morning Finally after 12 h of continuous wear CTT was equal to 41 27 mg/mm (15 81) corresponding to a decrease of 110 % in corneal sensitivity

One year interval

9 of the 12 subjects wearing hard contact lenses had participated in a similar experiment a year earlier (Millodot 1975) Their CTT had been determined

prior to inserting their lenses and after only 8 h of wear One year later their CTT was compared in the same conditions and the results are illustrated in Fig 3 The mean CTT (and SD) obtained prior to inserting the lenses were 19 33 mg/mm (5 43) in 1975 and 18 85 mg/mm (4 08) in 1976 This difference is not significant ($P > 0\ 25$) It gives an indication of the good reliability of the technique.

After 8 h of wear the mean CTT obtained in 1976 was 35 06 mg/mm (13 30) and in 1975 46 22 mg/mm² (18 24) However this difference is not significant using a paired samples t test ($P > 0\ 1$) In effect seven of the subjects exhibited an improvement whilst two showed some degradation

Effect of soft contact lenses

The corneal touch thresholds (CTT) obtained prior to inserting the lenses and after 4 8 and 12 h of continuous wear are shown in Fig 4 The mean CTT (and standard deviation) was found to be 30 8 mg/mm (14 22) in the morning This value is somewhat higher than with the other group because it included a larger number of older subjects (Boberg Ans 1955) as well as one aphakic patient (Schirmer & Mellor 1961) After 4 8 and 12 h CTT was found to be 37 87 mg/mm (12 78) 38 40 mg/mm (15 87) and 44 63 mg/mm (19 59) respectively The CTT was significantly different from what it was prior to

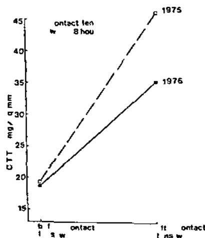


Fig 3

Corneal touch threshold (CTT) measured before and after 8 h of wear of hard contact lenses in the same group of subjects (N = 9) after an interval of one year

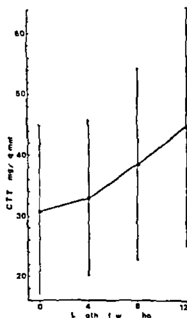


Fig 4

Relationship between the length of wear of soft contact lenses and peripheral corneal touch threshold (CTT) Each data point represents the mean of 15 subjects and the vertical lines represent ± 1 SD

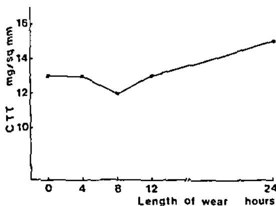


Fig 5

Effect of a high water content (85 %) soft lens on CTT as a function of the length of wear

inserting the lenses only after 8 h of continuous wear when corneal sensitivity (CTT [1]) was 25 % lower than what it was in the morning Corneal sensitivity continued to decrease and after 12 h of wear it was 45 % less on average than its value in the morning

It is worth noting that after 8 and 12 h of wear of soft lenses there were wide variations among the subjects Some subjects exhibited a large effect others none at all The reason for the large effect is attributed tentatively to what appears to be tight lenses although the subjects may have been wearing much thicker lenses but this is not known as it was not measured The lack of effect occurred in the patients wearing lenses with a high water content The results obtained on a patient wearing lenses with 85 % water content are shown in Fig 5 In addition to the usual measurements this patient agreed to wear his lenses continuously for 24 h and submit for one more measurement the next morning Only after that length of time was there any appreciable change in CTT in this subject

Discussion

The progressive diminution of corneal sensitivity with the length of wear of hard contact lenses indicates a continual and progressive interference of corneal metabolism Indeed an increase in corneal thickness has already been demonstrated (e g Miller & Exford 1967 Mandell & Polse 1970 Millodot 1975) as well as an increase in corneal oxygen uptake (Farris Kubota & Mishima 1971) It is interesting to note that this effect does increase throughout the length of wear of these lenses Thus it is not recommended to wear hard contact lenses for longer than one waking day However if the lenses are removed say after 10 h wear the cornea recovers most of its sensitivity very quickly as was shown by Millodot (1975)

Soft lenses also produce a progressive decline of corneal sensitivity but to a much lesser degree (< ⅓) than hard contact lenses And as pointed out above this effect is dependent upon the type of lenses Most corneal sensitivity also recovers very rapidly after removing these lenses (Millodot 1974) The interference with corneal metabolism induced by soft lenses has been documented (e g Bailey & Carney 1973) and it has also been found that corneal thickness increased as a function of the length of wear at least during a 12 h period of measurements (Polse Sarver & Harris 1975)

The results obtained with high water content lenses are very encouraging as it appears that these lenses have practically no effect on corneal sensitivity that is on metabolism throughout a day of wear As the nature of soft lenses

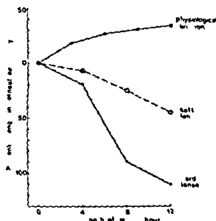


Fig 6

Mean per cent change in corneal sensitivity as a function of the length of wear of hard (N 1?) and soft (N = 15) contact lenses The physiological variation of corneal sensitivity measured throughout the same period of time by Millodot (19?) is also illustrated The 0 point along the abscissa corresponds to a time around 9 a m

plays an important role the least interference of corneal metabolism is provided by thin soft lenses with a high water contact

To facilitate the comparison between the effects of soft and hard contact lenses Fig 6 illustrates the per cent changes in corneal sensitivity as a function of the length of wear In addition this graph shows the physiological variation of corneal sensitivity throughout the same period of time (that is an increase throughout the day) using the data already obtained by Millodot (19?2) The true effects of contact lenses on the eye need to be compared against this physiological variation and not with the value of corneal sensitivity in the morning and therefore it is even greater than the actual percentages indicated above For example the effect of hard lenses after 12 h wear could be regarded as equal to 110 % plus 33 % which represents the physiological increase that would occur if that person did not wear contact lenses

The measurements after one year of wear of hard contact lenses indicate a possible adaptation but the measurements were not significant This conclusion applies at least to the small sample of 9 subjects used in this investigation and more measurements are needed before this problem can be solved unequivocally Farris Kubota & Mishima (1971) followed 10 volunteers for six months and found that in ?0 % of these cases there was a significant increase in corneal thickness after 8 h of comfortable contact lens wear This result is in good accord with the results of the present study

It has been shown clinically that hard contact lenses cause a central corneal oedema whereas soft lenses cause oedema which is evenly spread across the cornea (Mandell 19 6) Yet in this study corneal sensitivity was tested only in the periphery of the cornea (at 6 o clock) and marked changes were found with hard contact lenses Thus it seems as if the nerve fibers stimulated near the periphery reflect the activity occurring over a large corneal area Indeed there is some evidence that the sensory units of the cornea are quite extensive covering areas of 50 to 200 or more square millimeters (Tower 1940)

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THE EFFECT OF PROSTAGLANDIN ON IRIDIAL BLOOD VESSEL PERMEABILITY

BY

J SZALAY R GOLDBERG and R KLUG

Light and electron microscopy is used to examine the effect of exogenous PGE_1 on the permeability and reactivity of rat iridial blood vessels Results show that topical PGE_1 causes an increase in the permeability of iridial vessels to carbon particles (?00 Å diameter) The technique of carbon labelling is used to quantitate increases in permeability caused by varying concentrations of PGE_1 (0 001–1 0 mg/ml) Regression analysis shows that there is a linear relationship ($P < 0\ 02$) between carbon label ling and PGE_1 concentration over the range of concentrations tested In other experiments rats were treated with the systemic histamine libera tor Compound 48/80 or with topical applications of histamine diphos phate in order to examine the effects of exogenous and endogenous hista mine upon iridial blood vessel permeability These procedures produce only minimal labelling of irid al vessels It therefore seems likely that PGE_1 has a direct effect on iridial vessels and does not act indirectly by bringing about the liberation of endogenous histamine

Key words prostaglandin E_1 – iridial blood vessels blood aqueous bar rier – vascular inflammatory response – histamine – aging

Most of our information about the effects of prostaglandin on ocular blood vessel permeability has been obtained using the rabbit eye as an experimental system These experiments have shown that prostaglandin is present in the iris and is released into the aqueous following paracentesis (Ambache et al

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1965 Miller et al 1973) Furthermore exogenous prostaglandin causes an increase in the protein content of the aqueous (Beitch & Eakins 1969 Kelley & Starr 1971)

Although it is now clear that exogenous prostaglandin is capable of causing a breakdown of the blood aqueous barrier the major site of action of these fatty acid derivatives is still unclear Whitelocke & Eakins (1973) used intravenously injected sodium fluorescein to examine the permeability of rabbit iridial vessels before and after topical application of prostaglandin E_1 (PGE_1) and found an increase in the permeability of the iridial vessels Cole (1974) also used PGE_1 and sodium fluorescein and found little or no change in iridial blood vessel permeability The above conflicting results are undoubtedly a reflection of the fact that fluorescein angiography is not a reliable technique for detecting large scale changes in iridial blood vessel permeability (Szalay et al 1975)

The use of intravenously injected marker particles and fine structural studies have provided additional morphological information about the intraocular sites of action of prostaglandin Exogenous prostaglandins (E_1 and E_2) cause an increase in the permeability of both the blood vessels and the non pigmented epithelium of the ciliary body (Pedersen 1975a Vegge et al 1975) Thus it is now clear that in the rabbit the blood vessels of the ciliary body contribute in a major way to the breakdown of the blood aqueous barrier

Examination of the possible reactivity of rabbit iridial blood vessels to prostaglandin has yielded inconclusive results Using exogenous PGF_1 Cole (1975) found that iridial blood vessels remain impermeable to intravenously injected carbon particles Pedersen (1975b) on the other hand used exogenous PGF_1 and PGE_2 and found an increase in the permeability of these vessels to horseradish peroxidase (40 Å)

In the rat fine structural and light microscopic studies show that paracentesis also causes a breakdown of the blood aqueous barrier (Szalay et al 1975) and there is a marked increase in the permeability of the iridial blood vessels to carbon This increase in permeability is age related and greatest in older animals There is no evidence of an increase in the permeability of the vessels of the ciliary body Thus in the rat iridial blood vessels play a major role in contributing to the breakdown of the blood aqueous barrier induced by paracentesis These experiments did not determine whether endogenous prostaglandin was responsible for the iridial vascular response However pretreatment of the rats with aspirin a known inhibitor of prostaglandin synthesis (Vane 1971) resulted in a partial inhibition of the iridial inflammatory reaction

The present investigation is designed to determine whether exogenous PGE_1 is capable of inducing an inflammatory response in rat iridial blood vessels

In this regard it is important to examine the possibility proposed by Crunkhorn & Willis (1971) that PGE_1 induces inflammation in the rat by causing systemic histamine liberation We will also seek an explanation for the greater reactivity of iridial blood vessels of older animals following paracentesis

Materials and Methods

Immature and adult albino rats (CD COBS Charles Rivers Mass) were used Actual birth dates were available for all the one month old animals The ages of the remaining animals were obtained using histograms (provided by the breeder and pooled with our own data) correlating weight of this strain of rat with age Animals were anesthesized with sodium pentobarbital (40 mg/kg) Tail veins were cannulated with a Butterfly 23 G infusion set and the thin polyethylene tube allowed to retain 0 3 ml normal saline In some animals the saline solution contained 0 1 ml of heparin (2500 units/ml/500 g) Unless the use of heparin is specifically stated only saline was used A syringe containing a colloidal suspension of carbon was then connected to the polyethylene tube The anesthesized animal was placed on its side and the head propped up by cotton pads The blunt end (5 0 mm in diameter) of a stainless steel probe was then allowed to rest upon the cornea The probe was maintained in a vertical position by the experimenter This was done for 5 seconds five consecutive times Slight movements of the eye and probe with respect to one another resulted in a slight abrasion of the cornea This procedure was carried out in order to facilitate the penetration of substances across the corneal epithelium Drugs were then topically applied to the cornea

Topical application of drugs A drop of the test medium (PGE_1 histamine diphosphate saline or 0 2 M phosphate buffer pH 7 2) was placed over the cornea The head of the animals was always maintained in a horizontal position so that the cornea remained completely covered with the solution for the required amount of time (20 min for PGE_1 and 15 min for histamine) Many animals were used as controls and received only the topical application of saline or phosphate buffer In the experimental animals only one eye received the test drug and the other was left untreated as a control for the possible systemic effects of the test substances Test substances were gently blotted up with the rolled up edge of a kimwipe and carbon was injected The eye of the anesthesized animal was then observed under a dissecting microscope in order to observe the effects of the test substance on pupil size and iridial blood vessels

Carbon Prior to use stock colloidal suspensions of carbon (CII/1431A Special Pelikan Ink Gunther Wagner) were filtered through Whatman No 5 filter paper This solution was injected into the tail vein and carbon labelling was rated three hours after injection on a scale of 1 through 5 (Szaley et al 1975) This rating was done using the dissecting microscope and anesthesized animals Some eyes were then enucleated and the tissue processed as whole mounts or as epon embedded material (Szalay et al 1970)

Preparation and administration of test reagents Stock solutions of PGE_1 (Upjohn Co Kalamazoo Mich) contained 10 mg PGE/ml ethanol Dilutions of this stock were made using 0 2 M phosphate buffer pH 7 2 The stock and all dilutions were kept in the freezer and removed immediately prior to use Histamine diphosphate powder was stored in the freezer Solutions (2 0 mg/ml were made up in normal saline and administered to 6 animals (1–6 months of age) Compound 48/80 powder was stored in the freezer Solutions were made using saline Compound 48/80 was administered to 11 animals (1–6 months old) Five animals received intraperitoneal injections (0 5 mg/100 g) and six received intravenous injections (0 05 mg/100 g) When visible signs of swelling and/or reddening of the snout paws or ears were noted carbon was injected Control animals were injected with saline only Labelling was rated three hours later and tissue removed and processed as stated above In addition whole mounts of the cremaster muscle of the scrotum were prepared

Paracentesis Paracentesis was performed as described previously (Szalay et al 1975) using a 30 G needle to puncture the cornea The difference between the present experiments and those reported previously is that the present experiments are done in the absence of added heparin

Results

Controls No carbon labelling was observed in any of the control eyes or in the cremaster muscle of animals injected with saline

Paracentesis Animals subjected to paracentesis and injected with carbon and no heparin showed definite labelling of iridial vessels However in animals more than one month old this labelling was significantly lower than when heparin was injected along with the carbon (Fig 1) It is clear that in animals more than one month old heparin potentiates the carbon labelling induced by paracentesis

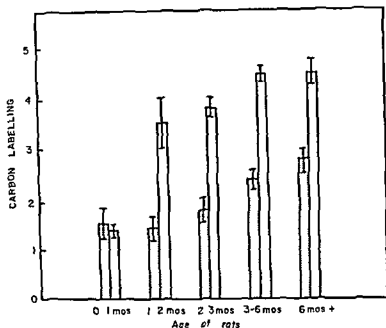


Fig 1

A histogram relating the age of the animal (in months) to the mean carbon labelling induced by paracentesis Stippled rectangles denote experiments done in the absence of heparin SE s are shown by vertical bars and are 0–1 month 0 29 1–2 months 0 24 2–3 months 0.25 3–6 months 0 21 6 months 0 25 *Empty rectangles are experiments* done with heparin and are regraphed from data shown in Fig 1 Szalay et al 1975 SE s are 0–1 month 0 17 1–2 months 0 50 2–3 months 0 24 3–6 months 0 17 6 months 0 25

Exogenous PGE_1 Twenty 1 month old animals received topical application of *four concentrations* of PGE_1 PGE_1 caused a marked dilation and engorgement of iridial blood vessels and these changes were not observed in the control eye Carbon labelling *occurred in the iridial vessels* of all experimental eyes Little or no labelling was seen in the ciliary body or limbus

Electron microscopic examination of carbon labelled *specimens enucleated* one hour after injection of carbon gave results that were indistinguishable from those obtained after paracentesis (Szalay et al 1975) Carbon particles were again present in enlarged spaces between adjacent endothelial cells and between the endothelial cell and its basement membrane

Fig 2 shows the effect of PGE_1 concentration on carbon labelling The correlation between labelling and the common log of prostaglandin concentration is 0 89 ($P < 0\ 01$) The regression of carbon labelling on PGE_1 concen

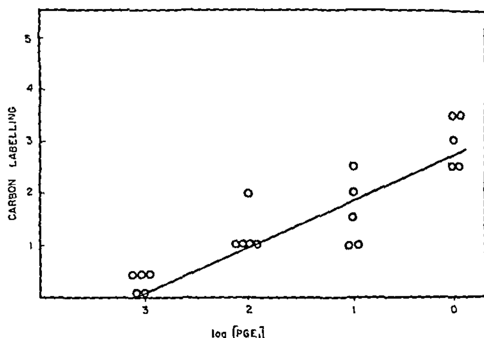


Fig 2

Dose response curve depicting the effect of varying concentrations of PGE_1 on iridial carbon labeling of twenty 1 month old animals The regression of carbon labelling on PGE_1 concentration is 0 85 ($P < 0\ 02$) The prediction equation for carbon labelling as a function of PGE_1 concentration is $y = 2\ 65 + 0\ 85\ (x_1)$ $s_{y\ x} = 0\ 51$

Table I

Intravenous injection	Carbon labelling	x	sε
Carbon and heparin	0 5 (1) 1 5 (4)	1 4	0 21
Carbon no heparin	1 0 (1) 2 0 (2) 3 0 (2)	2 5	0 40

Data depicting the effect of heparin on iridial carbon labelling induced by 0 01 mg/ml PGE_1 in 3–6 month old rats Column 2 gives the carbon labelling The number of animals is shown in parenthesis Column 3 gives the mean value for each group and column 43 gives the standard error Using the *t* test there was no significant difference between means

tration is 0 85 ($P < 0.02$) The prediction equation for carbon labelling as a function of PGE_1 concentration is $y = 2.65 + 0.85\ (x_1)$ The $s_{y \cdot x} = 0.51$ Thus there is a linear relationship between carbon labelling and PGE_1 concentration over the range tested

In another series of experiments ten animals (3–6 months old) were given topical PGE_1 (10 mg/ml) Half of this group was injected with carbon and heparin while the remainder received carbon only Table I compares the carbon labelling obtained under these conditions It is clear that heparin does not potentiate the carbon labelling induced by PGE_1

Compound 48/80 Compound 48/80 produced a visible edema of the snout ears and paws 15–30 min after injection The results were the same for animals receiving iv and ip injections Intravenous injection of carbon resulted in a blackening of the skin of the paws snout and ears In addition there was a marked carbon labelling of whole mounts of the cremaster muscle of the scrotum (Fig 3) Only minimal labelling was seen in iridial vessels (a mean labelling of +1) (Fig 4) and this labelling was the same in animals of all ages

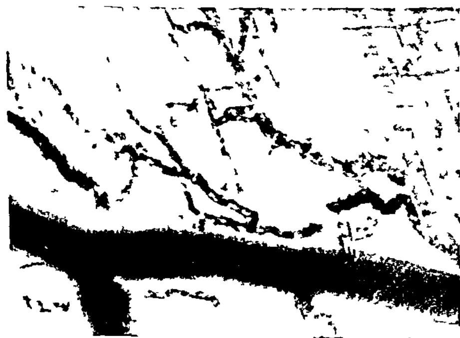


Fig 3
Light micrograph of the cremaster muscle of the scrotum. Carbon labelling was induced by injection of compound 48/80 Phase contrast × _0

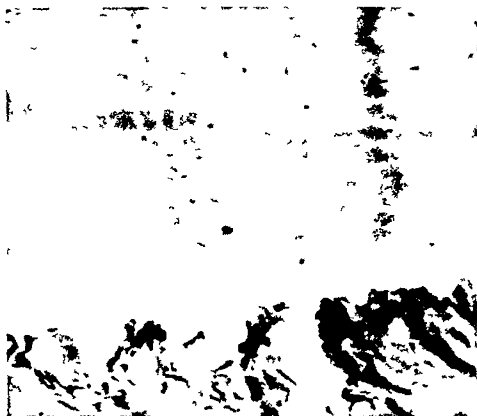


Fig 4

Light micrograph of the iris and ciliary body of an animal that had received an intraperitoneal injection of Compound 48/80 Note the marked labelling of the ciliary body and the minimal labelling of the iridial vessels Phase contrast ×220

Labelling of the ciliary body (Fig 4) and the vessels of the limbus was frequently observed

Topical histamine Topical application of histamine resulted in a minimal carbon labelling (mean = +1) of iridial vessels and this labelling was the same in animals of all ages

Discussion

Paracentesis produces a marked inflammatory reaction in iridial blood vessels of the rat This reaction is age related and greatest in animals more than 1 month old (Szalay et al 1975) In the paracentesis experiments the experi

mental protocol involved delays of up to 1.5 h between cannulation of the tail vein and the remainder of the experimental procedure. Heparin had therefore been used in the cannula to prevent blood clotting. Control experiments had shown that the injection of heparin along with carbon did not result in carbon labelling of iridial blood vessels. However, the present experiments show that in animals subjected to paracentesis the omission of heparin results in a significant decrease in carbon labelling of iridial blood vessels. Thus heparin potentiates the increase in iridial blood vessel permeability induced by paracentesis.

In experiments designed to determine whether prostaglandin is capable of increasing the permeability of iridial vessels we found that topical application of PGE_1 to the eyes of young and older animals results in a marked carbon labelling of the vessels. Light and electron microscopic observations show that carbon particles leave the lumen of the vessel through enlarged spaces between adjacent endothelial cells and accumulate beneath the basement membrane. Thus at the fine structural level PGE_1 is seen to induce an inflammatory vascular response indistinguishable from that produced by paracentesis.

Fig. 2 clearly shows that even in young animals iridial blood vessels are capable of undergoing a regulated and graded response to a wide range of PGE_1 concentrations. At all concentrations studied the increase in permeability allows for the escape of particles 200 Å in diameter across the vessel wall. In this respect it is interesting to re-examine the results obtained by Cole (1975). Cole found that iridial vessels of the rabbit remain impermeable to carbon after intracameral injection of PGE_1. However, we offer the following possible explanations for the discrepancy between those results and our own.

a) Species differences

In rabbit iridial blood vessels the gaps created between adjacent endothelial cells may only permit the passage of particles smaller than 200 Å in diameter.

b) Experimental differences

In our experiments the intraocular pressure is not maintained at a constant value and PGE_1 undoubtedly enhances the pressure gradient across the wall of the blood vessel. Minutes after its application PGE_1 induces a marked arteriolar and venular dilation causing a rise in the hydrostatic pressure within the small vessels of the microcirculation. Furthermore after 1.0 h the iris often displays a wrinkled appearance indicative of a drop in intraocular pressure. At this time the iridial vessels are still dilated. These conditions would enhance or perhaps create the formation of enlarged spaces between adjacent endothelial cells. In Cole's experiment the intraocular pressure was maintained at a constant value and the hydrostatic pressure drop across the wall of the vessel was probably minimized.



Fig 4
Light micrograph of the iris and ciliary body of an animal that had received an intraperitoneal injection of Compound 45/80 Note the marked labelling of the ciliary body and the minimal labelling of the iridial vessels Phase contrast × 220

Labelling of the ciliary body (Fig 4) and the vessels of the limbus was frequently observed

Topical histamine Topical application of histamine resulted in a minimal carbon labelling (mean = +1) of iridial vessels and this labelling was the same in animals of all ages

Discussion

Paracentesis produces a marked inflammatory reaction in iridial blood vessels of the rat This reaction is age related and greatest in animals more than 1 month old (Szalay et al 1975) In the paracentesis experiments the experi

PGE_1 also inhibits platelet aggregation (Samuelsson et al 1975) If under the conditions of our experiments PGE_1 has produced a near maximum inhibition of aggregation heparin would not be expected to produce an additional effect On the other hand PGE_2 does not inhibit platelet aggregation but (in the rat) stimulates it (Samuelsson et al 1975) Thus all of our experiments would be consistent with the hypothesis that in the rat PGE_2 is one of the predominant forms of prostaglandin liberated in response to paracentesis

Acknowledgments

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FREEZE FRACTURE REPLICA OF THE RAT CORNEA

BY

SATOSHI OKINAMI MASATO OHKUMA and ISAMU TSUKAHARA

The fine structures of the rat cornea with special reference to their intercellular junctions were studied using the freeze fracture technique At the corneal epithelium gap junctions could be observed between the adjacent cells At the stroma crater shaped depressions (between 300 and 500 Å in diameter) with pipe like appearing structures connecting the lamellae were found Intercellular junctions existing between the endothelial cells at the area near the anterior chamber are postulated to be the fascia (macula) occludens

Key words cornea freeze – fracture technique – zonula occludens – fascia occludens – gap junction – rat

The fine structures of the cornea have been documented by investigators who used a transmission electron microscope (Jakus 1954 1961 Sheldon 1956 Kaye & Pappas 1962 Iwamoto & Smelser 1965 Kaye Sibley & Hoefle 1973 Leuenberger 1973 Tonjum 1974 Iwata Uyama & Ohkawa 1975) however there are no reports of such observations using the freeze fracture technique In our study of the fine structures of the rat cornea in particular the intercellular junctions we used the freeze fracture technique and our findings are reported here

Material and Methods

The eyes of adult albino rats were enucleated under pentobarbital (Nembutal) anaesthesia and bisected at the equator thus making available the anterior

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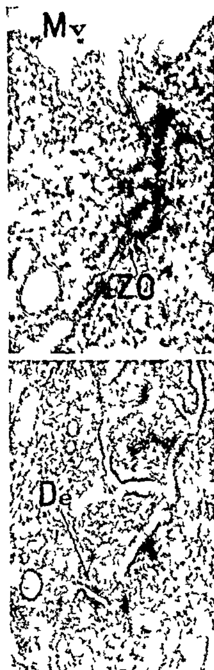


Fig 1

Corneal epithelium stained en bloc Micro villi (Mv) are visible Zonula occludens (ZO) can be seen along the lateral wall of the superficial cell near the surface ×110 000

Fig 3

Corneal epithelium stained en bloc Desmosomes (De) are visible between the epithelial cells ×36 800



Fig 9

Freeze fracture replica of the corneal epithelium Three epithelial cells (EP) are visible Many microvilli (Mv) are visible in the anterior cell membrane of the superficial layer ×19 550

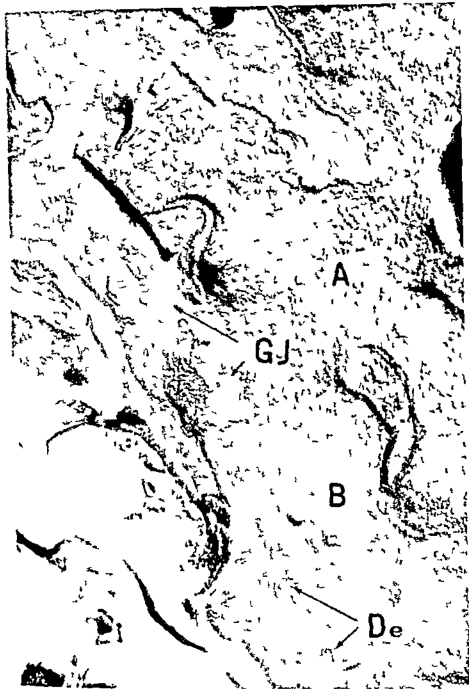


Fig 4

Freeze fracture replica of the corneal epithelium. These are exposed faces of cell membrane revealed by being split between the epithelial cell membranes A number of clusters of fine particles (De) corresponding to desmosomes and typical gap junctions (GJ) are visible on the surfaces of the epithelial cells A fracture face A B fracture face B ×6 500

halves These tissues were fixed with 4 % glutaraldehyde in a phosphate buffer (pH 7 2) for one h After washing with a buffer they were immersed overnight in 40 % glycerol in distilled water The cornea was cut into small pieces and then set in the lower half of a paired metal block (developed by Nishiura 1972) which was placed directly in liquid nitrogen (–196°C) The metal block containing the tissue specimens was then transferred into the bell jar of a vacuum evaporator in which a high vacuum level exceeding 3×10^{-6} Torr was achieved Sliding the upper half of the metal block was actuated and the specimens contained in the cavity of the lower half were cleft resulting in exposure of their freeze fracture face Shadowing with platinum paladium and carbon was then carried out at an angle of 45° on the freeze fractured tissue surface and additional carbon coating was applied at an angle of 90° The specimens were then bleached in distilled water at a room temperature of 20°C and replicas were obtained After repeated washing in distilled water the specimens were placed on copper grids and observed under a transmission electron microscope (Hitachi HU–11A or 11D)

For comparison other enucleated eyes were fixed in 2 % osmium tetroxide solution for one h Cell junction specimens were then stained en bloc with uranyl acetate for 3 h These specimens were dehydrated in graded alcohols and embedded in Epon 812 Ultrathin sections cut on an ultramicrotome and stained with uranyl acetate and lead citrate were examined under a HU–11A or HU–11D (Hitachi) electron microscope

Results

The corneal epithelium of rat is composed of 5–12 cell layers The anterior cell membrane of the superficial cell layer has numerous microvilli and microplicae (Figs 1 and 2) The zonula occludens can be seen along the lateral walls of the superficial cells near the surface (Fig 1) Desmosomes were fre

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Fig 5

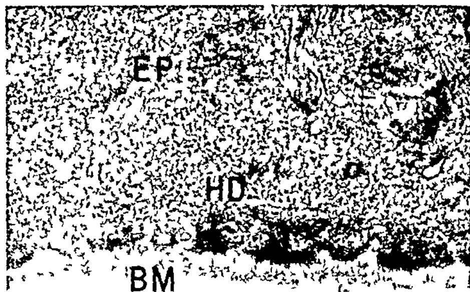
Freeze fracture replica of the corneal epithelium Nuclear pores (NP) are evident in the corneal epithelium nucleus (N) The basement membrane (BM) appears to be homogeneous × 10 350

Fig 6

Freeze fracture replica of the corneal epithelium and stroma The surface of the basal cells (BC) adjacent to the basement membrane (BM) is rough Structures corresponding to half desmosomes are not evident × 31 050

5

6



La
K

quently observed between the epithelial cells (Fig 3) With the freeze fracture technique a number of clusters of fine particles (somewhat smaller than 90 Å particles of the gap junction) which correspond to desmosomes were found at the surface of epithelial cells and typical gap junctions were also visible (Fig 4) The gap junction had an aggregation of 90 Å particles on fracture face A and corresponding pits on fracture face B (McNutt & Weinstein 1970) Nuclear pores were observed in the corneal epithelium nucleus but they were few in number and the basement membrane separating the basal cells from the stroma appeared to be homogenous (Fig 5) The surfaces of the basal cells were drawn out into many finger shaped processes which interdigitate with processes of the adjacent cells and surfaces of basal cells adjacent to the basement membrane were observed to be rough (Fig 6) Numerous half desmosomes were evident along the basement membrane (Fig 7) No structure corresponding to half desmosomes was evident herein (Fig 6)

Collagen fibrils run parallel in the stroma and are uniform in size and spacing Lamellae are composed of groups of these collagen fibrils and it is noteworthy that circular crater shaped depressions (between 300 Å and 500 Å in diameter) were evident on the fracture face when the fracture plane runs between the lamellae (Figs 8 and 9) These crater shaped depressions are assumedly short channel like structures connecting the lamellae which are composed of collagen fibrils Fibroblasts (keratocytes) were also frequently observed between the lamellae (Figs 8 and 10) Nuclear pores of the fibroblast were few in number (Fig 10)

Descemet s membrane which is a basement membrane of endothelial cells is homogenous in appearance and although somewhat thicker is much like the basement membrane of the epithelial cells Structures specific to the tight junction can be observed at the area near the anterior chamber and between the endothelial cells (Fig 11) Ridges which are specific to the tight junction are seen here and as they appear to be discontinuous may be the fascia (macula) occludens

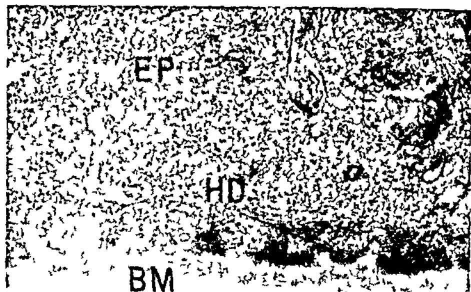
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Fig 7

Corneal epithelium (EP) stained en bloc Along the basement membrane (BM) numerous half desmosomes (HD) are seen. × 36 800

Fig 8

Freeze fracture replica of the stroma Between the lamellae (La) crater shaped depressions (arrows) and fibroblast (keratocyte) (K) are visible × 10 3o0



La
K



DM
N
TJ
AC
11

Fig 10

Freeze fracture replica of the stroma. Keratocyte is visible between the lamellae (La) Nuclear pores of the keratocyte nucleus (KN) are few in number × 1[illegible]0

Fig 11

Freeze fracture replica of the corneal endothelium and Descemet s membrane. Descemet s membrane (DM) is homogeneous in appearance Between the endothelial cells (EN) structure specific to the tight junction (TJ) is visible at the area near the anterior chamber (AC) Ridges (arrow) are visible but appear to be discontinuous 23 000

Discussion

Elements of the intercellular junctions are identified as tight junction (zonula occludens fascia occludens) zonula adhaerens (intermediary junction) and macula adhaerens (desmosome) (Farquhar & Palade 1963) In thin sections prepared by the en bloc staining method the tight junction is characterized by fusion of the adjacent cell membranes resulting in obliteration of the inter cellular space The tight junction is divided into the zonula occludens and the fascia occludens In the zonula occludens continuous attachment around the total surfaces is visible and in the fascia (macula) occludens discontinuous attachments are observed

Another histological approach to the study of the corneal permeability is the method using electron microscopic tracers (horseradish peroxidase and lanthanum nitrate) As these tracers penetrate the intercellular spaces of the corneal endothelium (Iwamoto & Smelser 1965 Kaye Sibley & Hoefle 1973 Leuenberger 1973) junctions seen at the area near the anterior chamber are not considered to be the zonula occludens but rather discontinuous tight junc tions termed the fascia (macula) occludens With the freeze fracture technique this observation is also supported by the fact that the ridges appear to be discontinuous and few in number

As tracers injected into the anterior chamber stopped at the junctions of the superficial layers of the corneal epithelium (Tonjum 1974 Iwata Uyama & Ohkawa 1975) the zonula occludens may indeed exist in this area Iwata et al (1975) reported not only the existence of the zonula occludens at the outermost cell layer of the corneal epithelium but also the existence of the occludens type junctions in the neighbouring cell layers In other words it is considered that the zonula occludens is at the outermost cell layer of the corneal epithelium while the fascia (macula) occludens is in the superficial half of the squamous cell layers The structure of the tight junction in the corneal epithelium could not be demonstrated using the freeze fracture technique as the course of the plane of fracturing cannot be controlled but from our many years of research concerning this aspect we are under the impression that there is no tight junction except at the outermost cell layer of the corneal epithelium

The gap junction resembling the tight junction in thin sections has been demonstrated to be the site of electronic coupling (Revel & Karnovsky 1967 Revel Yee & Hudspeth 1971) The possibility of the gap junction at the corneal epithelium was first suggested by Hogan (1971) and existence of this junction was confirmed in the present study

Channels can be frequently seen between groups of the lamellae of the stroma and may appear empty or to contain granules or cells i e corneal corpuscles or

Schwann cells (Jakus 1954) The freeze fracture technique revealed crater shaped depressions or elevations on the fracture face when the fracture plane runs between the lamellae These depressions described here for the first time with our application of the freeze fracture technique resemble fenestrations of the endothelium of the choriocapillaris and probably are pipe like structures connecting lamellae of the stroma Whether or not such depressions play an important role in the permeability of the stroma is now under investigation

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ORBITAL INVOLVEMENT BY PLASMACYTOMA

Report of Two Cases

BY

EEVA NIKOSKELAINEN ANGELOS DELLAPORTA
THOMAS RICE BARBARA EGBERT and BARTON LANE

Two patients with orbital involvement of plasma cell myeloma are presented. The first patient presented an isolated plasmacytoma in the orbit the second patient had generalized plasma cell myeloma In both cases X rays and computed tomographic scanning gave valuable information and biopsy confirmed the diagnosis

Key words orbita – plasmacytoma – tomography

Plasma cell myeloma usually arises from the bone marrow occasionally from extraosseous tissues Sometimes myeloma presents itself as an apparently single skeletal lesion termed plasmacytoma In most cases plasmacytomas ultimately develop disseminated disease (Clarke 1953 Blodi 1975 Busse et al 1975 McFadzean 1975 Rodman & Font 1972) Clarke divides orbital myelomas into two categories – those originating in the orbit and those which involve the orbit secondarily (Clarke 1953)

In this paper the clinical features of two cases with orbital plasma cell myeloma are described The first patient had a solitary plasmacytoma in the orbit the second presented secondary involvement of the orbit by generalized plasma cell myeloma

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was palpable near the temporal superior margin of the orbit The patient reported pain on pressure below the middle of the right eyebrow Slit lamp examination showed mild conjunctival chemosis and some irregularity of the epithelium of the upper third cornea of the right eye The refractive media were clear and the fundus normal The applanation tension was 19 in each eye The corrected visual acuity was R E 20/40 J6 and L E 20/20 J1 The pupils were of equal size and both direct and consensual reaction to light was normal The visual fields on the Goldmann perimeter were normal The left eye was normal

Radiographic studies including skull and sinus series demonstrated an extensive destructive process involving the right supra orbital ridge adjacent frontal bone the lateral margin of the right frontal sinus and probably the supra orbital ethmoid sinus in this region The roof of the orbit and the zygomatic process of the frontal bone as well as the lateral extremity of the lesser wing of the sphenoid also showed patchy destruction. The optic foramen and superior orbital fissure were normal Computed tomographic scanning of the orbit (Fig 1 A 1 B) confirmed the proptosis of the right eye. The optic nerve was displaced medially by a soft tissue mass in the right postero lateral orbit which became denser following intravenous contrast material The lateral wall of the orbit was destroyed by the tumour There was no extension of the tumour into the brain Brain scan showed increased radioactivity in the flow and static views over the area of the right orbit

Orbitotomy revealed a large bony defect of the lateral two thirds of the orbital roof and the upper one third of the lateral orbital wall by a grey tumour Biopsy specimen showed sheets of plasma cells with characteristic eccentric nuclei nuclear chromatin pattern and juxtanuclear zones Some of the cells were binucleated and others had prominent nucleoli MGP stains showed uniform pyroninophilia (Fig 2) The histological diagnosis was plasmacytoma There were no other bone involvements

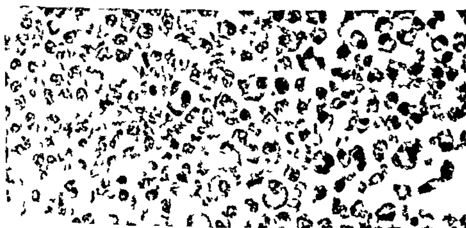


Fig 2

Microscopic section of orbital biopsy in high power view reveals characteristic morphology of plasma cells with cartwheel chromatin eccentric nuclei binucleation and juxta nuclear clear zones (Haematoxylin and Eosin, x 480)



Fig 3
Computerized tomographic scanning of the orbits and maxillary antra

A Scanning at the level of the maxillary sinuses demonstrates a soft tissue mass filling the right antrum with extension medially into the nasopharynx (between arrows)

B 5 mm above scan A the tumour extends into the floor of the orbit posteriorly (arrow)

Chest X ray was normal Serum and urine protein studies were negative for para proteins Bone marrow biopsy from the iliac crest was normal The impression was that the patient had isolated plasmacytoma in the right orbit with no evidence of systemic involvement

Five thousand rads of radiotherapy were given to the right orbit and the sinuses which subsequently led to regression of the proptosis

Case 2 A 48 year old white male presented in December 1972 with a mass on his forehead which had an underlying lytic lesion Biopsy showed plasma cell myeloma. It was treated successfully with radiation The patient was asymptomatic until September 1973 when he presented with partially collapsed vertebra T 7 He was treated with bedrest melphalen and prednisone with symptomatic improvement. In April 1975 he manifested pancytopenia He suffered further compression of vertebra T 7 and

developed neurologic signs of motor weakness in the left lower extremity At this time he was treated with pelvic traction prednisone melphalen blood transfusions and radiation therapy 500 rads were administered to the thoracic vertebrae and 1000 rads to the mass on his sternum with good results

In July 1975 the patient was referred to the eye clinic because of increased tearing and blurred vision in the right eye of one month duration and diplopia of three days duration His face was asymmetric with increase in the right nasal labial fold He had a 9 mm proptosis of the right eye There was moderate restriction of eye movements upwards and to the right both associated with diplopia No tumour or bony defects were palpable Slit lamp examination showed slight conjunctival chemosis in the right eye The refractive media were clear The pupils were of equal size and both direct and consensual reaction to light was normal Fundus examination showed choroidal folds extending from the right optic disc to the macula Numerous drusen were around the macula in both eyes Otherwise the fundi were normal The visual acuity was 20/20 J1 in both eyes The visual fields with the Goldmann perimeter were normal

Radiographic studies of skull orbits and facial bones showed extensive permeative lucencies involving the entire cranial vault as well as the right maxilla and mandible There was marked demineralization of the dorsum sellae The right maxillary antrum was opaque and the medial lateral and posterior walls were destroyed The roof of the antrum was markedly elevated by the underlying tumour There were soft tissue densities in the anterior ethmoids and posterior sphenoid sinuses Chest X rays showed multiple destructive rib lesions with associated extrapleural densities consistent with the diagnosis of plasma cell myeloma Bone survey for metastases showed diffuse involvement of all of the visualized bones Computed tomographic scanning demonstrated a soft tissue mass in the right maxillary antrum extending superiorly into the posterior orbit (Fig 3 A 3 B) A second soft tissue mass in the right orbit was seen more superiorly behind the globe (Fig 4)



Fig 4
Computerized tomographic scanning at the level of the upper third of the orbits shows a second mass seen behind the right globe (arrowhead) No bony destruction or intra cranial tumour is identified

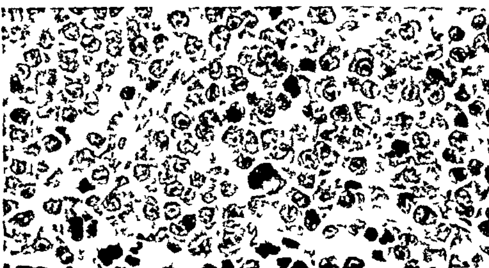


Fig 5

Microscopic section of maxillary sinus biopsy High power details show some cells with characteristic features of plasma cells others with large atypical nuclei (Haematoxylin and Eosin x 480)

In July 1975 the patient had a biopsy of the tumour extending into the right nasal cavity as well as biopsy of the right maxillary tumour The biopsies showed multiple fragments of atypical plasma cells with large nuclei with prominent nucleoli and abundant pyroninophilic cytoplasm (Fig 5) The features were similar to those of a previous bone marrow biopsy consistent with plasma cell myeloma

The right cranial sinuses were irradiated with 4000 rads One month after radio therapy there was marked resolution of the proptosis In November 1975 there was no proptosis and no restriction of the movements of the right eye

Discussion

According to Rodman & Font (Rodman & Font 1972) the incidence of orbital involvement in plasma cell myeloma is rare It has to be differentiated from benign plasma cell accumulations which are produced by chronic inflammation (Reese 1964) In the present paper two patients with orbital plasma cell myeloma were presented Blurred vision increased tearing diplopia and drooping of the upper eye lid and proptosis were the presented symptoms Computed tomographic scanning of the orbit is a new method to investigate orbital lesions (Gawler et al 1974 Momose et al 1975) In both cases this method gave valuable information of the extent and localization of the tumour Biopsy confirmed the diagnosis in both patients

The first patient had solitary orbital plasmacytoma without evidence of generalized disease Extended follow up and detailed postmortem studies have proven that solitary extramedullary plasmacytoma presents the first stage in generalized disease Later patients develop other signs of plasma cell myeloma (Clarke 1953 Rubenzik & Tenzil 1975 Williams et al 1972) Therefore patients with orbital plasmacytomas have to be followed for generalized disease

The second patient developed orbital involvement as a complication of generalized plasma cell myeloma The prognosis of this disease has improved during the last few years (Williams et al 1972) With the present therapeutic regimens significant degrees of improvement or remission can be achieved in at least 60 to 80 per cent of all patients with plasma cell myeloma (Williams et al 1972) In both presented cases radiotherapy led to marked improvement of orbital involvement

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UNILATERAL PROPTOSIS DUE TO MIDBRAIN TUMOUR

A Case Report

BY

A R CHOUDHURY J C TAYLOR and R WHITAKER

A case of unilateral proptosis attributed to midbrain tumour is reported The proptosis disappeared after release of intracranial hypertension The postulated mechanism of the unilateral proptosis on the left side is a relative increase in orbital venous stasis on that side consequent upon intracranial hypertension

Key words midbrain tumour – intracranial hypertension – unilateral proptosis – exophthalmos

Unilateral proptosis in intracranial tumours is caused by a relative increase in orbital content Tumours about the cavernous sinus may produce ipsilateral proptosis either by their invasion of the orbit (Jackson 1962 Choudhury 1973) or by the production of orbital venous stasis (Dixon 1941 Meadows 1944) In 1948 Gardner reported a case of unilateral exophthalmos which was due to the raised intracranial pressure occurring in a haemangiomatous cyst of the cerebellum in this case the exophthalmos was caused by an encephalocele in the orbit through its roof which was absorbed following a previous fracture Here we report a case of unilateral exophthalmos which was due to raised intracranial pressure occurring on a midbrain tumour and venous stasis in the orbit

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Case Report

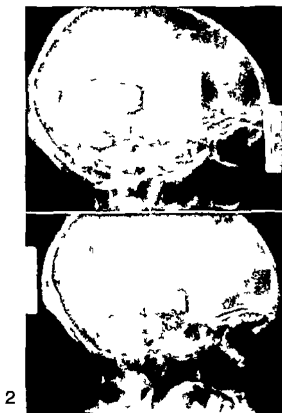
A 50 year old man was referred to us because of a three month's history of progressive diplopia and this was associated with dimming of vision in the left eye which was also protruding Simultaneously he developed increasing weakness of the right arm and leg and increasing tremor of the right hand Three years previously in 1971 he was investigated elsewhere for progressive diplopia right sided hemiparesis and tremor of the right hand The diplopia disappeared after two months but the hemiparesis and the tremor improved but persisted There was no history of headache or vomiting nor was there any story of fits

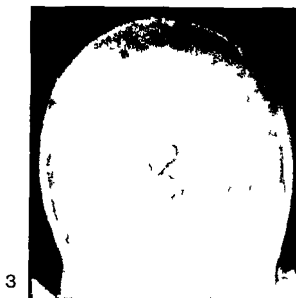
On admission he was normotensive (190/80) there was a right sided spastic hemi paresis, ataxia of the right arm and leg together with static and intention tremor of the right hand. There was obvious left sided proptosis which was non pulsatile and it could be pressed back into the orbit after some initial resistance. The optic discs were oedematous The visual fields were normal but the visual acuity was reduced to N 18 in the left eye Exophthalmometric readings were 16 mm for the right eye and 21 mm for the left eye. The left eye was displaced upwards 2 mm and temporally 4 mm The diplopia was present on left lateral gaze and on elevation and depression of the globes and there was marked limitation of vertical conjugate movements of the eyes with loss of convergence In view of this combination of signs a clinical diagnosis of intrinsic midbrain neoplasm was made The ataxia of the right arm and leg and static and intention tremor of the right hand were thought to be due to the involvement of the right superior cerebellar peduncle Plain radiographs of the skull and chest were normal and so also was the brain scintiscan The carotid angiograms (Fig 1) showed outward displacement of the thalamostriate veins indicating ventricular dilatation. This was confirmed by myodil ventriculogram (Figs 2 and 3) which also showed a rounded defect in the left side of the floor of the IIIrd ventricle The origin of the



Fig 1

Bilateral carotid angiogram showing increased bowing of the thalamostriate veins indicating hydrocephalus





Figs 2 and 3

Antero posterior and lateral views of myodil ventriculogram showing a mass indenting the left side of the body of the third ventricle with irregularity of the aqueduct

aqueduct was displaced to the left and looked irregular This suggested a tumour of the midbrain extending up the pedicle into the basal ganglia with possible cyst indenting the IIIrd ventricle The hydrocephalus was treated by a ventriculo atrial shunt because of the inaccessible and inoperable nature of the tumour

Post operatively there was a dramatic improvement in ocular features On the day following operation there was some conjugate vertical eye movement and improvement in the proptosis was noticed At the time of discharge a week later there were full conjugate eye movements the proptosis had disappeared and the optic discs became clear and the visual acuity in the left eye returned to N 8 The diplopia was present only at extreme elevation and depression of the globes on left lateral gaze The exoph thalmometric readings were 16 mm for the right eye and 17 mm for the left eye which was no longer displaced either vertically or horizontally Although there was little improvement in pyramidal and cerebellar signs the patient felt subjectively much improved Follow up at three months showed no change in neurological signs and at six months showed deterioration in neurological signs Exophthalmometric readings remained unchanged on both occasions (16 mm for the right eye and 17 mm for the left eye)

Discussion

This patient presented with unilateral proptosis and evidence of a midbrain intrinsic neoplasm as shown by pyramidal signs ataxia and vertical gaze palsy Bilateral papilloedema was also present as a definitive sign of raised intracranial pressure The diplopia might have been caused by limitations of movements of the left eye which were mechanically induced i e attributed to the considerable proptosis of that eye Interestingly headache and vomiting were persistently absent He had apparently enjoyed a remission in symptoms three years earlier and such improvement in intrinsic brain stem neoplasm has been previously reported (Walton 1971) Recent worsening of the symptoms was due to the progression of the growth which had produced narrowing of the aqueduct of Sylvius and thus partially obstructed the CSF circulation with consequent ventricular dilatation and raised intracranial pressure Return of conjugate vertical eye movements and convergence following release of the intracranial hypertension suggests the compression of the midbrain tectum by third ventricular distension (Shallat et al 1973)

There was no evidence of intraorbital disease and the unilateral proptosis is therefore attributed to the intracranial hypertension We suggest the mecha nism to be orbital venous stasis from raised intracranial venous pressure con sequent on intracranial hypertension The disappearance of proptosis and papilloedema following release of intracranial hypertension supports the venous hypothesis The temporal and upward displacement of the globe of the left eye were presumably a mechanical effect due to bulk of orbital veins lying

medially and inferiorly in the orbit Abolition of such displacements following release of intracranial hypertension supports this view

The unilateral nature of the exopthalmos is very dependent on the variability of the venous drainage of the cavernous sinuses which form the final common pathway for antegrade and retrograde venous flow from and to the orbit respectively The venous system is remarkably variable thus the cavernous sinus may fail to develop in one side or the other (Hamby 1966) or the venous drainage of one sinus may predominantly be to the other side (Pool & Potts 1965) We believe that the venous drainage in our case is probably directed towards the left cavernous sinus from the right thus giving rise to increased orbital venous stasis on the left side and unilateral proptosis

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ORBITOGRAPHY WITH A NEW NON IONIZING WATER SOLUBLE CONTRAST MEDIUM

BY

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Metrizamide is a non ionic water soluble contrast medium which is iso tonic with human blood and tissue fluid at a concentration of 170 mg I/ml Retrobulbar injection of 3 ml isotonic metrizamide in the muscular conus of rabbits causes slight and inconstant cellulitis but a similar reaction can also be found after injection of the same amount of saline It seems probable that the introduction of fluid sufficient to cause an increase in the retrobulbar pressure can cause inflammatory changes in the orbital tissue and that this is not always caused by the contrast medium itself Four patients were examined by orbitography with injection of 4 ml iso tonic metrizamide There were no side effects and the orbitograms showed contrast of good quality Metrizamide is therefore considered very suitable for orbitography especially in hospitals where computer tomography is not yet available

Key words orbitography – contrast media – metrizamide – amipaque – retrobulbar cellulitis

X ray investigation of the content of the orbit has been difficult and inadequate because the soft tissues in the orbit are surrounded by bony walls The methods which have been used for study of the contents of the orbit are internal carotid arteriography phlebography via the frontal or the infraorbital vein and

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pneumography combined with tomography Several authors have described these methods among them Decker (1955) Herbert et al (1956) Bertelsen & Petersen (1957) Decker & Schlegel (1957) Lombardi (1957) Du Boulay (1961) Bertelsen (1962) de Raad (1964) and Enge & Bergaust (1970) but the adverse effects have sometimes been serious (Sachsenweger 1958 Lombardi 1967 Lombardi & Passerini 1968 1969)

Metrizamide (trade name Amipaque) is a water soluble tri iodinated contrast medium that was introduced a few years ago for neuroradiological examinations Its neurotoxicity is less than any other water soluble contrast medium in use (Skalpe 1974 Oftedal 1975) It has a low osmolality because no dissociation takes place in solution and a concentration of 170 mg I/ml is isotonic with human blood At the Department of Diagnostic Radiology Ullevaal Hospital University of Oslo we have for some years used metrizamide experimentally for studying its effects and toxicity in angiography (Skalpe & Evensen 1972) in endoscopic retrograde pancreatography (Lilleås & Swensen 1976) and in arthrography (Johansen & Berner 1976) The purpose of this study was to ascertain whether metrizamide is a suitable contrast medium for orbitography

Material

The material consists of nine albino rabbits of both sexes with a mean weight 3650 g and four patients two male and two female in whom removal of one eye was planned because of suspected malignant disease

Methods

Under nembutal anaesthesia five animals were injected with 3 ml isotonic metrizamide (170 mg I/ml) in the muscle conus on one side and 3 ml meglumine calcium metrizoate 170 mg I/ml (Isopaque amin 200 mg I/ml diluted with distilled water) on the other side In one animal 5 ml of each contrast medium was injected The injections were performed during TV fluorscopy and control roentgenograms were taken to ensure correct disposition of the contrast media In two animals 3 ml of 0 9 % saline were injected on each side One animal was not injected and served as control

Of the animals injected with 3 ml contrast media three were sacrificed after one day and two after one week The animal injected with 5 ml contrast media the two injected with saline and the control animal were sacrificed after one day The orbital contents were removed fixed with buffered 3 5 %

formalin and sections were prepared and stained with eosin and haematoxylin. The histological sections were examined by the pathologist without prior knowledge of which agents had been injected.

The clinical examinations were performed with the patient in the supine position. 4 ml isotonic metrizamide was injected slowly into the muscular cone by puncture through the lower eyelid without local anesthetic. Frontal and lateral roentgenograms were taken on the skull table, and frontal and lateral tomography was then performed with a polytome with hypocycloid movements.

Results

All the bulbi oculi in the rabbits were histologically normal. Of the retrobulbar contents slight infiltration of inflammatory cells were found in two cases where 3 ml metrizamide had been injected, one of the animals was sacrificed



Fig. 1 A

4 ml isotonic metrizamide in the muscle conus of left orbit. Frontal view. The optic nerve clearly seen in centre of the orbit. The impressions of the different eye muscles and the lacrimal gland is clearly seen.



Fig 1 B
The same patient lateral view The dorsal part of the eye with a normal optic nerve demonstrated (These structures marked out with a pencil)

after one day and the other after one week Somewhat more marked cell infiltration and slight focal muscular cell degeneration in extra ocular muscle was seen in the case where 5 ml of contrast was injected and the response was greater with metrizoate than metrizamide Slight cellulitis was also found in three of the four orbital contents where physiological saline had been injected

In the four patients who were submitted to orbitography with metrizamide the contrast was rather rapidly reduced with blurring of outline after 20 min None of the patients complained of pain and the small amount of contrast did not cause any exophthalmus or other visible changes in the eye or its surroundings In one patient (Fig 2) a man 71 years old who had unilateral exophthalmus an expansion was demonstrated which we considered to be a tumour of the lacrimal gland At surgery no tumour was found Instead a diffuse soft tissue swelling corresponding to the X ray findings was seen This patient has not had any complication due to the injection of metrizamide



Fig 2 A and B

A Tomography frontal view of patient with enlarged lacrimal gland with diffuse soft tissue swelling

B Same patient tomography lateral view The posterior part of the eye with the optic nerve marked out with a pencil

Discussion

Manchester et al (1955) found cases of necroses in the sclerae after injection of 1 ml of diodrast (a water soluble contrast medium) in the muscular conus of rabbits All rabbits injected with 2 ml or more of diodrast showed more severe damage of the bulbi and orbital cellulitis No histological changes could be found after injection of 1 ml saline

We found no cases of damage of the bulbi However a slight and inconstant orbital cellulitis occurred when 3 ml of metrizamide was injected Similar changes were also seen after injection of the same amount of physiologic saline It seems probable that such reaction is due to the introduction of an amount of fluid sufficient to cause an increase in the retrobulbar pressure and proptosis with impairment of circulation More marked reaction in retrobulbar tissues was seen after injection of 5 ml of contrast media

Lombardi (1967) reported his experience with 150 orbitographies He used a tri iodinated contrast medium diluted with 1 ml of anaesthetic and with distil led water to a concentration of about 20 % After retrobulbar anaesthesia

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FURTHER DATA ON BIOMETRIC CORRELATIONS OF CENTRAL CORNEAL THICKNESS

BY

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Central corneal thickness measured in 126 young men aged from 18–21 years was correlated to a number of ocular and other parameters The frequency distribution was skewed towards the lower end but the deviation could not be statistically supported No correlation between corneal thickness and birth weight was found Other characteristics not correlated in this material to corneal thickness were corneal astigmatism refraction visual acuity optic disc and retinal abnormalities red green colour vision defects ABO and rhesus blood groups EEG abnormalities chromosomal abnormalities hearing defects ear abnormalities and quality of the hair The findings in this study although mainly of negative character stress the relative independence of the central corneal thickness as a biometric parameter

Key words biometry – corneal thickness – birth weight – blood groups – astigmatism – refraction – ophthalmoscopy

Since the development of good optical pachometers the biometric correlations of central corneal thickness (CCT) have been studied No correlations have been found between CCT and depth of anterior chamber lens thickness length of vitreous body or axial length of the eyeball (Ehlers Kruse Hansen & Aasved 1975) After a small but significant reduction during the first years of life (Ehlers Sorensen Bramsen & Poulsen 1976) the CCT has not been found

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to be correlated to age (Kruse Hansen 1971) In the study of Kruse Hansen (1971) there was a tendency towards decreasing thickness with increasing body height although this was not statistically significant

The present report is concerned with data obtained on examining a number of young men all prisoners at Møgelkær during the years 1969–71 Various data were available as the eye examination was part of a large socio medical study which will be presented in detail elsewhere

Material and Methods

The study comprised 1?6 young men aged from 18–21 years all prisoners at Møgelkær a state prison for young criminals The series therefore cannot in all respects be considered as representative of young danish men The 101 were included in the above mentioned comprehensive socio medical investigation performed in the period August 1969–April 1971 Twentyfive were subjected to eye examinations only and were those already imprisoned at Møgelkær when the socio medical study was started

The eye examination comprised determination of visual acuity refraction slit lamp biomicroscopy ophthalmoscopy and campimetry 6/2000 white The external eyes were inspected and the occurrence of squint was evaluated by the cover test Central corneal thickness (CCT) was measured with a Haag Streit pachometer and corneal curvatures and astigmatism by a Haag Streit keratometer Screening for red green colour vision defects was made with the Ishihara plates

As there is a strong right left correlation for CCT and additionally in this study a systematic difference between the two eyes the left cornea being measured thicker the numerical analysis presented below apply to right eyes only Inspection of the figures for the left eyes treated statistically in a similar manner revealed no new information

Results

Central corneal thickness (CCT)

The average CTT was for right eyes 0 514 ± 0 0027 (mm ± SEM) The frequency distribution curve is shown in Fig 1 The shape of the histogram might suggest some abnormal cases at the lower limit but this cannot be supported statistically the marginal items are at mean value minus 2 standard deviations outside which some 2 5 % would be expected Neither did the Kolmogorov Smirnov test show any deviation from the normal curve

Correlations of CCT

This part of the study comprised only the 101 subjects of the socio medical study The analysis was performed by cross tabulating CCT against various

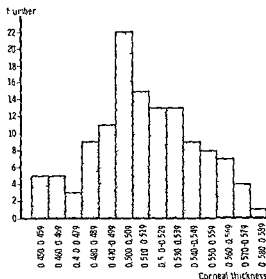


Fig 1
Frequency distribution for central corneal thickness in 126 young men
Corneal thickness in mm

Table 1
Central corneal thickness (CCT) and birth weight

Birth weight grams	2000 -2499	2500 2999	3000 3499	3500 3999	4000 4499	4500 4999	> 5000	no inform	Total
CCT mm									
< 0 450	1	1	1	4	2	–	–	3	12
0 480–0 499	–	1	2	3	1	–	1	2	10
0 500–0 539	1	6	13	12	5	1	–	13	51
0 540–0 559	–	1	2	3	3	–	–	4	13
> 0 560	–	2	4	3	–	1	–	3	13
no inform	–	1	–	1	–	–	–	–	2
Total no	2	12	22	26	11	2	1	25	101

Data for right eyes

properties including all registered properties that might influence or be in fluenced by the CTT

Birth weight Table I shows that there is no evident correlation between CCT and birth weight This might have been expected as the cornea is thick at birth and particularly thick in premature babies (Ehlers et al 1976)

Ocular parameters Cross tabulations revealed no correlation between CCT and astigmatism refraction or visual acuity Ophthalmoscopical abnormalities of the optic disc vessels or retina showed no correlation to CCT Red green colour vision defects were not correlated to CCT

Other characteristics ABO and Rhesus blood groups showed no correlation with CCT (Table II) EEG abnormalities were noted in 39 cases no correlation to CCT could be demonstrated Chromosomal abnormalities were found in 11 cases normal thickness was found in cases characterized as 47XXY $46XY16GH^+$ $46XY9GH^+$ $46XYGP^+$ Six cases were $46XYQ^+$ of these 3 had a normal CCT while 3 showed a CCT below 0 48

Hearing defects ear abnormalities and quality of the hair (silky normal stiff) showed no correlation to CCT

Discussion

In spite of the fact that most of the observations in this study are of a negative character i e show no correlation to the CCT it was found worth while to briefly present the results as part of our continued studies of corneal thickness

Table II
Central corneal thickness (CCT) and ABO blood groups

Blood groups	A	B	O	AB
CCT mm				
< 0 480	8	1	3	–
0 480–0 499	2	–	7	1
0 500–0 539	15	5	31	–
0.540–0.559	7	2	4	–
> 0.560	5	3	5	–
no inform	1	–	1	–

The average thickness conforms with previous findings (Kruse Hansen 1971 Ehlers et al 1975) The frequency distribution although suggestive of a surplus of low values did not differ from a normal distribution The thickness distribution has been studied in a group of 90 conscripts and in 146 recipients of kidney grafts Deviation from a normal distribution could not be demonstrated although in the latter group two maxima could be suggested (Ehlers et al 1976)

A correlation between CCT and birth weight could have been expected when it is recalled that the newborn has a thicker cornea than children and adults A particular thick cornea is found in premature babies The lack of correlation suggests that general growth is not the factor determining the thickness change after birth but rather that the thickness is controlled by more specific effects as previously discussed (Ehlers et al 1976)

The correlations to the various ocular and other parameters were studied in a search for the characteristics of the CCT The results have been negative and as such hardly require further comment It should however be stressed that the lack of correlation illustrates a relative independence of the CCT which tends to make this an interesting and unique parameter

Acknowledgments

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TRANSIENT GLAUCOMA AS A MANIFESTATION OF MUMPS

A Case Report

BY

WERNER POLLAND and WILLIAM THORBURN

A case report of a 43 year old man who during convalescence after mumps (parotitis epidemica) developed bilateral glaucoma associated with redness of his eyes but no other ocular manifestations The chamber angles were open. No signs of scleritis or iritis were present The best treatment was found to be prednisolone topically and acetazolamide orally After ten days the intraocular pressure was normalized and after a fortnight all treatment could be discontinued.

Key words mumps – epidemic parotitis – glaucoma transient

Case Report

A 43 year old man with a family history of glaucoma was seen at the Umeå University Eye Clinic complaining of slight pain and redness of the eyes of two to three days duration Increasingly hazy vision had been noted the last day There was no history of any previous eye disease Four weeks prior to admission he had been exposed to mumps and was given mumps hyperimmune globulin two days after exposure A serological test at the same time showed no immunity against mumps Seventeen days later he showed typical symptoms of mumps with swelling and tenderness of the parotid and submaxillary glands

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and fever One week after the onset of his illness the fever and swelling of the glands subsided and he began to notice his eye symptoms There were no symptoms of orchitis

Mumps serology during convalescence showed a significant rise in antibody titre

The physical findings were identical in both eyes Uncorrected distant vision was 20/20 each eye At first sight the bulbar conjunctiva showed a uniform increased redness There was no discharge or local tenderness The pupils were slightly wider than normal but reacted briskly The appearance was similar to that of viral conjunctivitis Slitlamp examination showed that the redness was due to an increased vasodilatation of the superficial vessels with no episcleral component The corneae were slightly steamy without signs of keratitis There were no cells or flare in the anterior chambers No corneal precipitates or anterior lens surface exfoliations were seen Gonioscopical examination showed wide open chamber angles with no pigment increase or anterior synechiaes

The optic discs had physiological cups There were no signs of papilloedema or papillitis Tension measured with applanation tonometer was 40 mmHg in the right eye and 39 mmHg in the left eye

Initially the patient was given 500 mg acetazolamide orally and pilocarpine 4 % eye drops Next morning the intraocular pressure was reduced in both eyes but in spite of continued 4 % pilocarpine topically three times a day in

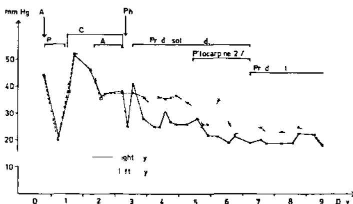


Fig 1

The course of the intraocular pressure (ordinate) from the day of admission (abscissa) during different treatments

O d = right eye O s = left eye O a = both eyes P o a = Pilocarpine 4 % instilled in both eyes C o a = Carbachole 3 % instilled in both eyes Az = acetazolamide orally Ph = 10 % phenylephrine in the right eye Further comments in the text

both eyes the pressure rose again to about 50 mmHg (Fig 1) A change of miotics to 3 % carbachole had no obvious effect Acetazolamide 0 25 g x 3 added from the second day again reduced the tension This therapy was discontinued after one day Instillation of 10 % phenylephrine in the right eye three times with five min intervals resulted in a transitory normalizing of the tension The therapy was then changed to 0 5 % prednisolone topically five times a day in the right eye and no treatment in the left eye The next day the tension in the right eye was 10 mmHg lower while the tension in the left eye was unchanged During the following two days 2 % pilocarpine three times a day was administered in the left eye with little effect as shown in Fig 1 He was then given prednisolone 0.5 % topically three times a day in both eyes On the ninth day the IOP was normalized in both eyes and soon afterwards all therapy was discontinued

Further follow up during the course of one year showed normal tension and no further need for therapy The optic discs and the visual fields remained quite normal

Discussion

Several ocular manifestations of mumps are known dacryoadenitis optic neuritis keratitis conjunctivitis scleritis and iritis (Riffenburgh 1961) The occurrence of elevated intraocular pressure without signs of iritis has not been described previously In fact to the best of our knowledge there are only two cases of secondary glaucoma reported (Riffenburgh 1954 Roussel 1946) These were in conjunction with iritis and affected mainly one eye The occurrence of glaucoma without signs of flare cells or precipitates has not been described earlier

It is known that in scleritis a secondary rise of tension is a frequent complication Several cases of scleritis following mumps are described (Berg 1927 North 1953 Swan et al 1962) but no rise in tension was noted in these cases In the present case no sign of scleritis was observed

A transient rise in the intraocular pressure during convalescence after mumps might easily be overlooked As a rule when a young person is affected a slightly red eye and some pain might be misinterpreted as a conjunctivitis Therefore it is possible that this complication is sometimes overlooked

The different treatments of the elevated intraocular pressure showed that miotics alone did not reduce the pressure A good response was obtained with acetazolamide as well as transitorily by the frequent instillation of 10 % phenylephrine (Fig 1) Prednisolone topically promptly reduced the tension

The conclusion drawn is that the treatment of choice is acetazolamide orally combined with prednisolone topically Probably glaucoma of this kind will revert spontaneously We think the use of topical steroids reduces the duration of the increased intraocular tension

It is interesting to speculate on the pathogenesis of the increased tension in this case A reasonable explanation is a reduced outflow of aqueous humour due to an increase in resistance in the structures of the chamber angle This idea is supported by the prompt reduction of the pressure by steroids Predniso lone might reduce oedema of the trabecular meshwork resulting in an increase in the facility of outflow of the aqueous humour

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THE CYCLOPENTOLATE PROVOCATIVE TEST IN SUSPECTED OR UNTREATED OPEN ANGLE GLAUCOMA

IV Fluorescein Angiography of the Vessels of the Iris in Open Angle Glaucoma Eyes with a Positive Cyclopentolate Response

BY

OLAVI VALLE and ANTTI VANNAS

Fluorescein angiography of the iris (IFAG) was performed on 15 patients with a positive cyclopentolate response (IOP elevation $\geq$ 8 mmHg) in 17 eyes to the cyclopentolate provocative test The chamber angles were open in all the eyes Seven of the responder eyes had capsular glaucoma undergoing treatment, six had simple glaucoma two had pigmentary glaucoma and two suspicion of open angle glaucoma

The object was to study with IFAG whether vascular changes can be established in the iris of the responder eyes such as could have a role in the elevation of IOP

All the eyes with capsular glaucoma displayed vascular changes vaso proliferation and fluorescein leakage from the iris vessels No other vascular changes were seen in the irises of the responder eyes IFAG revealed no differences in the iris vasculature between responder and non responder eyes A vascular aetiology for the IOP elevation in responders is improbable

Key words cyclopentolate – fluorescein angiography – intraocular pressure – iris – mydriasis provocative test – open angle glaucoma – pseudo exfoliation.

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Intraocular pressure (IOP) may rise significantly also in open angle eyes during the mydriasis provocative test One of the authors established an IOP elevation ≥ 8 mmHg in the cyclopentolate provocative test (CPT) in 21 (4 9 %) of 431 eyes with suspected or untreated open angle glaucoma (Valle 1976a) The most notable group among the responder eyes consisted of eyes with pseudoexfolia tion (PE) and open angle glaucoma (Valle 1976b)

The mechanism of IOP elevation in responder eyes is inadequately known Pigment plays a role in the IOP elevation in a part of the cases (Kristensen 1965 1968 Aggarwal & Beveridge 1971 Valle 1976c) It is possible that in addition to pigment PE material raises IOP in pseudoexfoliation eyes (Kristen sen 1965 Valle 1976b)

Significant vascular changes in the anterior parts of the eye have been en countered in conjunction with the PE syndrome Vannas (1969 1972) demon strated vascular proliferation and fluorescein leakage from the blood vessels in PE eyes on fluorescein angiography of the iris (IFAG) The number of radial vessels in the iris is also often reduced Electron microscopic (EM) studies have shown (Shakib et al 1965 Ringvold 1969 1970 Vannas 1972) an abnormal basement membrane in the iris vessels The basement membrane is thin or absent in places and there is abnormal extracellular material around the vessels The vascular endothelium is thin and fenestrae are seen in some cases (Vannas 1972) Layden & Shaffer (1974) were unable with light and electron microscopy to demonstrate definitive changes in the basement mem brane of iris vessels in two PE eyes

Eyes with capsular glaucoma have displayed vascular changes also in peri limbal vessels in both FAG (Laatikainen 1971) and EM studies (Ringvold 19 ? Layden & Shaffer 1974) Ringvold (1973a) detected PE material also extra bulbarly around the conjunctival vessels of the palpebrae

In the present study IFAG was performed on eyes which had previously given a positive response (IOP elevation ≥ 8 mmHg) to CPT although the chamber angles were open all the time The purpose of the study was to find out whether it is possible with this method to establish vascular changes in the iris of responder eyes which might be of etiological importance for the IOP elevation in responder eyes

Patients and Methods

IFAG was performed on 15 patients 17 of whose eyes responded to CPT with an IOP elevation ≥ 8 mmHg Fifteen of these 17 eyes had open angle glaucoma under treat ment two involved suspicion of open angle glaucoma Seven of the eyes with open

angle glaucoma had capsular glaucoma six had simple glaucoma and two pigmentary glaucoma

The IFAG was done at the iris angiography laboratory of the Eye Clinic University of Helsinki the method has been described elsewhere (Vannas 1969) Both simple glauc ma and capsular glaucoma eyes served as controls (Vannas 1969) In 11 of the responders the fellow eye was used as control six of which gave a negative response (IOP elevation ≤ 4 mmHg) to cyclopentolate and five of which were border line cases (IOP rise 5–7 mmHg) IFAG and serial photography of the iris and peri limbal vessels were always performed first on the responder side

Two patients had mild diabetes mellitus without diabetic retinopathy or rubeosis Not a single eye displayed occlusion of the central vein or artery

Results

The findings for the 17 cyclopentolate responder eyes examined by IFAG were as follows

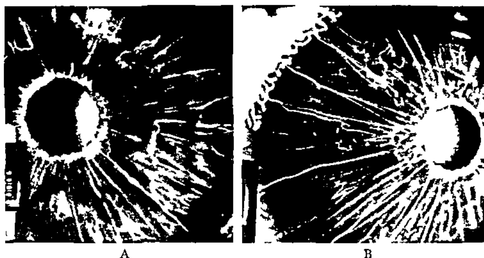
Capsular glaucoma (seven eyes) Six eyes revealed vascular changes such as fluorescein leakage at the pupillary border Five eyes displayed fluorescein leakage also in the ciliary region Vasoproliferation was present in all the eyes (Fig 1 A and B) The authors considered the number of radial vessels to be reduced in two eyes The iris vessels were not visualised in one darkly pig mented eye

Simple glaucoma (six eyes) IFAG was normal in four eyes In two eyes fluo rescein leakage on the pupillary border but not in the ciliary region was seen There was no vasoproliferation The arteries of two eyes were notably thick In one of these two eyes capillaries were visualised distinctly in the pupillary region A couple of vascular tufts with some leakage of dye were seen in the same area (Fig 2 A)

Pi mentary glaucoma (two eyes) IFAG was normal The vessels of the iris were well visualised (Fig 2 B)

Suspected open angle glaucoma (two eyes) IFAG was normal for one of the eyes which had prominent vessels and a v loops on the pupillary margin The iris vessels of the other eye were not visualised because of abundant pigmenta tion

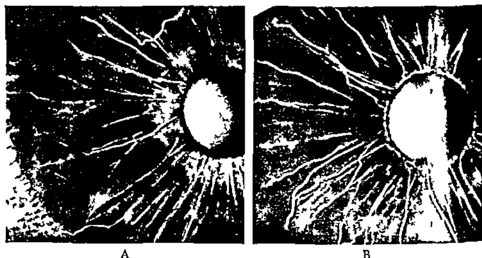
Fellow eyes of the responders (11 eyes) No demonstrable differences were seen in IFAG compared with the contralateral responder eyes



A B

Fig 1

Vasoproliferation and fluorescein leakage in both the ciliary and pupillary region in two cyclopentolate responder eyes with capsular glaucoma
A female aged 75 right eye B male aged 80 left eye



A B

Fig 2

A Male aged 59 Right eye simple glaucoma and positive response to the cyclopentolate provocative test Prominent arteries no vasoproliferation Capillaries visualised distinctly in the pupillary region A few vascular tufts with some fluorescein leakage
B Female aged 46 Right eye pigmentary glaucoma and positive response to the cyclopentolate provocative test Normal IFAG Well visualised iris vessels

Discussion

Despite the numerous studies the origin and the histochemical nature of PE material are still unclarified (Blackstad et al 1960 Ashton et al 1965 Horven 1966 Layden & Shaffer 1974) PE material possibly contains acid mucopoly saccharide (Dvorak Theobald 1954 Gifford 1957 Arnesen et al 1963) and tyrosine (Dvorak Theobald 1954) According to Bertelsen & Ehlers (1969) PE material contains tyrosine and tryptophan but not acid mucopolysaccharide and lipids It is protein like histochemically and is probably not an acid mucopolysaccharide (Bertelsen et al 1964) It contains fibrillary protein (Dark et al 1969) or at least some protein (Ringvold 1973b) It has also been shown histochemically that PE material resembles glyco or mucoprotein (Bertelsen 1966 Horven 1966) or amyloid (Ringvold & Husby 1973)

The PE syndrome was recently observed in one clinical and five autopsy cases in connection with hereditary systemic amyloidosis with lattice corneal dystrophy (Meretoja & Tarkkanen 1975) These eyes revealed histochemical evidence of amyloid deposits in PE material present in the ciliary body capsule of the lens and on the surface of the iris The authors stressed the necessity of using a staining method sensitive to Congo red for the histochemical demonstration of amyloid (Puchtler et al 1962) and a special polarisation microscope for the demonstration of red green dichroism They like Ringvold & Husby (1973) considered that the negative results for amyloid previously reported in connection with PE (Busacca 1927 Horven 1966 Bertelsen & Ehlers 1969 Ringvold 1972) are explained by the different methods employed

The vascular changes seen on IFAG in the present responder eyes with capsular glaucoma confirm earlier studies in which vasoproliferation and fluorescein leakage have been found to be closely associated with PE (Vannas 1969 1972 Cobb & Smith 1970) No specific vascular changes were demonstrated in the eyes with simple glaucoma These meagre findings on IFAG are in accordance with earlier observations in simple glaucoma eyes (Vannas 1969) The vascular tufts at the pupillary border which were seen in a 59 year old non diabetic patient (Fig 2 A) are common in older persons especially in diabetics (Cobb 1968 1971) Vascular tufts at the pupillary margin of patients over 60 were reported by Cobb (1971) in 25 % of diabetics and 5 % of non diabetic patients

It has not proved possible so far to establish in PE eyes whether vascular changes or PE material develop first However structural changes and fenestrae have been demonstrated in the vascular wall of newly formed iris vessels It is possible that the changes in question alter the blood aqueous barrier and

may thus cause changes in the viscosity of the aqueous humour but considered as a whole are hardly decisive

IFAG was normal (Fig 2 B) for one patient who had pigmentary glaucoma and whose eyes both responded positively to CPT

Vascular changes associated with capsular glaucoma could be confirmed with this method They did not however differ in these CPT positive eyes from the familiar disease picture of pseudoexfoliation Furthermore no anatomic changes in the vessels of the iris were established in the eyes with simple glaucoma It is probable that a positive response to cyclopentolate is not due to structural changes in the iris vessels

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THE CYCLOPENTOLATE PROVOCATIVE TEST IN SUSPECTED OR UNTREATED OPEN ANGLE GLAUCOMA

V Statistical Analysis of 431 Eyes

BY

OLAVI VALLE

The mydriasis provocative test with 1 % cyclopentolate (CPT) was performed on 431 eyes with suspected or untreated open angle glaucoma Tonography was performed both before and during CPT to study the changes in aqueous dynamics during the test Statistical analysis of the results yielded the following mean trends and correlations at a highly significant level ($P < 0\ 001$) in the alterations

Intraocular pressure (IOP) rose ($\Delta P \pm$ SD) (+1 4 ± 2 9 mmHg) and aqueous outflow facility decreased (ΔC) (–10 %) during CPT The distribution of ΔP and ΔC did not follow the normal Gaussian distribution The change in ΔP deviated from the Gaussian distribution in 5–10 % of the eyes The deviating values concur with those of the responder eyes in which IOP rose ≥ 8 mmHg during CPT ΔP was linearly dependent on the initial IOP level P_0 and the absolute change was always almost constant, ~ +1 4 mmHg Both the total series and the responder eyes displayed the same trend for the change in aqueous outflow facility in relation to the initial C value (C_0) low C_0 values changed less on average and high C_0 values changed more and diminished It is not known why the ΔC change was different depending on the C_0 value The change in IOP correlated statistically highly significantly with the initial C value (C_0) The lower the C value the higher was the mean IOP elevation during CPT In contrast the change in aqueous outflow (ΔC) did not correlate (N S) with the initial IOP level (P_0) before CPT

Key words cyclopentolate – intraocular pressure – mydriasis provocative test – open angle glaucoma – suspicion of open angle glaucoma

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As reported in an earlier paper (Valle Part I 1976a) the mydriasis provocative test with 1 % cyclopentolate (CPT) was performed on 218 patients 431 eyes with suspected or untreated open angle glaucoma Twenty one eyes (4 9 %) gave a positive response during the test with intraocular pressure (IOP) rising ≥ 8 mmHg (responders) The chamber angles were open throughout the test The CPT was negative for the majority of the eyes (82 6 %) with IOP failing to rise appreciably (≤ 4 mmHg) or falling (non responders) The mean IOP change (M ± SD) during CPT was +2 5 ± 3 1 mmHg in the glaucomatous group (196 eyes) +0 4 ± 2 5 mmHg in the group with suspicion of open angle glaucoma (235 eyes) and +1 4 ± 2 9 mmHg in the total material The difference in the IOP change between the glaucoma group and the suspected group was statistically highly significant ($P < 0\ 001$)

Several authors have reported a decreased aqueous outflow facility (outflow) during the mydriasis provocative test with both parasympatholytics (Galin 1961 Schimek & Lieberman 1961 Christensen & Pearce 1963 Šmeral et al 1964 Barany & Christensen 1967 Iwata et al 1968 Makabe 1968 1969b c 1970 Étienne 1972) and sympathomimetics (Lee 1958 Kristensen 1968 Makabe 1969b 1970) In the present research project the effect of cyclopentolate on the aqueous dynamics was studied on the same patients by performing tonography before CPT and a second time during the test The aqueous outflow and inflow were both impaired on average statistically highly significantly ($P < 0\ 001$) during the test in the total series (260 eyes) (Valle 1974) The outflow deteriorated relatively evenly in all the groups though most in responder eyes (by an average of 20 %) but the difference from the non responder eyes was not statistically significant ($P > 0\ 05$) In contrast a statistically significant ($P < 0\ 01$) difference between responder and non responder eyes was observed in the inflow change It increased in the responder eyes but decreased fairly clearly in the non responders The difference in the changes in aqueous inflow between the responders and the non responders – with outflow impairing concomitantly – is considered primarily to account for the notable IOP elevations during CPT (Valle 1974)

In addition to these previously published results and analyses it was considered warranted to make a statistical analysis of certain variables for the total series What happens in the eyes of the total material during CPT? How does IOP change (ΔP) during CPT independently of the initial IOP level? How does the aqueous outflow change (ΔC) regardless of the initial C value (C)? Do the distributions of ΔP and ΔC differ from the normal Gaussian distribution? Do ΔP compared with the initial IOP level and ΔC compared with the starting C value conform to a mathematical law? How does IOP change (ΔP_0) during CPT in relation to the initial aqueous outflow value (C)?

How does the aqueous outflow change (ΔC) in relation to the IOP level (P) before CPT? A statistical analysis of these questions is interesting not least because to the best of the author s knowledge no such analysis has been per formed in earlier studies of a corresponding nature

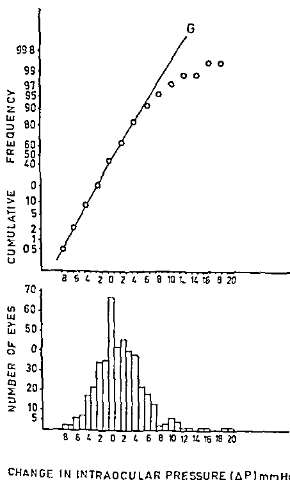


Fig 1

Bar graph (lower set) and cumulative % frequency plot (upper set) of the distribution of maximal changes in intraocular pressure (ΔP) during the cyclopentolate provocative t s in the total series of 431 eyes The data are represented in two forms one above the other with a common scale at the abscissa G = Gaussian distribution

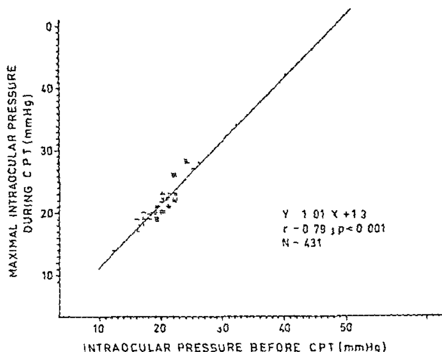


Fig 9
Distribution of intraocular pressures before and of maximal changes (ΔP) during the cyclopentolate provocative test (CPT) in 431 eyes

Patients Methods and Criteria

The patients and the methods and criteria applied in the study were the same as were described in detail in Part I of the study (Valle 1976a) The total material thus comprised '18 patients with suspected or untreated open angle glaucoma in one or both eyes in all 431 eyes

Details of the performance of tonography before and during CPT have been described elsewhere (Valle 1974) Although the intention was to perform tonography on all the eyes before CPT and again 1½–? hours after the beginning of the test the latter examination in particular was not made in some cases for various reasons The most important reason why only 260 eyes were included in the study on the aqueous dynamics during CPT was the requirement that the tonographic tracings on both examinations had to be technically successful for reliable comparison No other selective criteria were applied to this material Even then it is the most comprehensive material reported in the literature concerning tonographies performed in connection with the mydriasis provocative test

Statistical methods Linear first order least squares regression analysis was used for the statistical analysis of the results The regression equation the correlation coefficient (r) and its significance (P) and the number of observations (N) were entered in the figures

Results

Fig 1 shows graphically the distribution of the maximal IOP changes (ΔP) during CPT for the total material regardless of the initial IOP level A general trend observed is a statistically highly significant ($P < 0.001$) rise (+1 4 ± 2 9 mmH) in ΔP To facilitate the visual inspection the normal Gaussian distribution was plotted linearly (G) by the method described by Armaly (1967) on a probability paper in the upper set of Fig 1 The distribution points show that the distribution of ΔP is not normal but skewed to the right The deviation

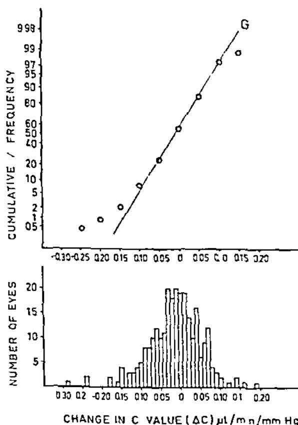


Fig 3

Bar graph (lower set) and cumulative % frequency plot (upper set) of the distribution of changes in outflow coefficient (ΔC) during the cyclopentolate provocative test in 60 eyes The data are represented in two forms one above the other with a common scale at the abscissa G = Gaussian distribution.

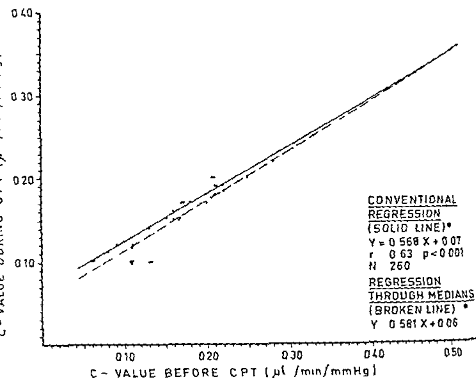


Fig 4

Distribution of outflow coefficients before and of changes (ΔC) during the cyclopentolate provocative test (CPT) in 260 eyes

* Conventional least squares regression line

Regression line calculated with the least squares method using 10 median values of the Y variable in 10 intervals of the X variable (see the text)

begins at a frequency of 90–95 % corresponding to the responder group (cf the lower set) Thus in 5–10 % of the eyes ΔP changes differently from the normal Gaussian distribution

An analysis is made in Fig 2 of whether ΔP compared with the initial IOP level (P_o) observes a mathematical conformity to law ΔP in the present material is in linear correlation with P_o An absolute change is always almost constant ~ +1 4 mmHg independently of P_o The lower the P_o the lower is the maximal IOP level (P_{max}) during CPT The higher the P_o the higher is P_{max} The following formula is obtained $P_{max} = (P_o + +1\ 4)$ mmHg

Fig 3 presents graphically the distribution of the changes in aqueous outflow (ΔC) during CPT in 260 eyes irrespectively of the C value before CPT

The general trend observed is a mean statistically highly significant ($P < 0\ 001$) decrease (−0 07 ± 0 05) with 10 % in the C value Fig 3 has two sets similarly to Fig 1 The upper set shows that the distribution of ΔC is not consistent with the normal Gaussian distribution The distribution points reveal a deviation to the left at a frequency of 10 % and the distribution is moreover a little too wide at the ends to be normal In ~ 10 % of the eyes ΔC decreases more than in the normal distribution

In contrast, there were also cases in which ΔC increased considerably during CPT as is seen in the lower set of Fig 3

Does the distribution of the changes in aqueous outflow (ΔC) during CPT compared with the C value before CPT (C) observe some mathematical conformity to law? Fig 4 answers this question in the affirmative The regression lines show that a low C value changes during CPT differently on average from the change of a high C value When C is low (< 0 14) ΔC changes less

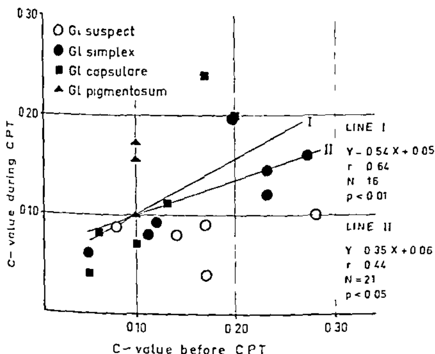


Fig 5

Distribution of outflow coefficients before and of changes (ΔC) during the cyclopentolate provocative test (CPT) in 21 eyes with a positive cyclopentolate response Line I 16 open angle glaucoma eyes Line II All 21 responder eyes

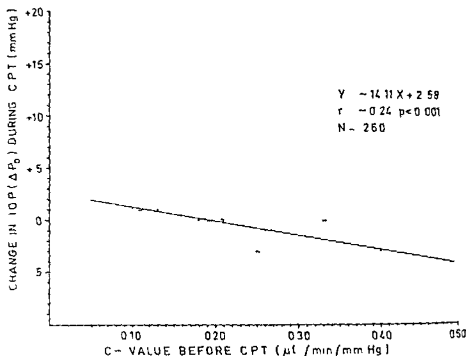


Fig 6

ati in between outflow coefficient before the cyclopentolate provocative test (CPT) and change in intraocular pressure (ΔP_0) during CPT in 260 eyes

and the mean C value increases When C_o is high (> 0 14) the C value changes more and decreases The higher the C_o value the more ΔC decreases

There was some asymmetry in the C value distributions during CPT when crutinized at different intervals of the C value before CPT The rela tionship between the two was therefore explored not only by conventional linear regre sion but also by (1) grouping the C value before CPT into 10 intervals (0–0 04/0 05–0 09/0 10–0 14/0 15–0 19/0 20–0 24/0 25–0 29/0 30–0 34/0 35–0 39 0 40–0 44 0 45–μl/min/mmHg) (2) calculating the medians of the C value during CPT in these intervals and (3) calculating the equation of the regression line with Y = weighted medians of C during CPT and X = corre sponding interval centre values of C before CPT This procedure was con sidered to give a more realistic average trend than the conventional regression procedure Both lines are depicted in Fig 4

It was interesting in this context to analyse correspondingly the distribution of ΔC during CPT in 21 responder eyes in relation to the C_o value As can be seen from Fig 5 ΔC changed in this group in the same way as in the total

material A similar trend in the changes of ΔC was even more accentuated in the responder group than in the total series A low C value signifies a small change in C value a high C_o value suggests a pronounced decrease in the C value during CPT The trend of the changes in C value appears clear also in the five responder group eyes with suspected glaucoma However the material for responder group eyes with suspected glaucoma is too small to warrant any conclusions

Fig 6 show how IOP changes (ΔP) during CPT in relation to the aqueous outflow value before CPT (C_o) A definite trend is observed When C_o is low ($<0\ 19$) IOP rises during CPT the more clearly the lower the C_o value When C is high ($>0\ 19$) IOP falls on average during CPT the more distinctly the hi her the C value

Fig ι reveals how aqueous outflow changes (ΔC) in relation to the IOP level before CPT (P) ΔC is not dependent on the initial IOP level and it does not change as a function of P_o ΔC may decrease or increase but it happens independently of P_o The regression line approaches zero regardless of the P level

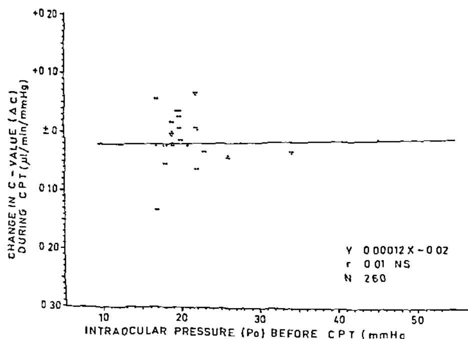


Fig ‑

Relation between intraocular pressure (P_o) before the cyclopentolate provocat ve test (CPT) and change in outflow coefficient (ΔC) during CPT n ιJ eyes

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THE VARIATION AND COVARIATION OF CUP AND DISC DIAMETERS

BY

BO BENGTSSON

The variation and covariation of cup and disc diameters were studied in a material derived from a population survey and consisting of 2,334 fundus photographs from as many eyes in 1,322 subjects. A simple device was used to facilitate focusing of the camera. The colour slides were projected on to a screen at a fixed distance and measured on ruled paper. The effect of refraction on the magnification in the eye-camera system was compensated by the use of a simple correcting factor. Some apparently quite normal discs nevertheless had an area more than four times larger than that of other equally normal ones. The sizes of discs and cups covaried, however, to a surprisingly great extent ($r = 0.8$) and changes in disc diameter were in general paralleled by similar changes in cup diameter. The amount of tissue in the optic nerve head therefore varied somewhat less than the disc size. Cup diameters were widely dispersed, unevenly distributed and heavily dependent on disc size. The average rim breadths, on the other hand, were much less dispersed, normally distributed and independent of the disc diameter. By taking the covariation of cup and disc diameters into account, the detection of any enlargement or diminution of the optic cup ought to be facilitated.

Key words: cup diameter – disc diameter – average rim breadth.

There is unanimous agreement that excavation of the optic nerve head is typical of advanced glaucoma with extensive visual field loss. The enlargement of the optic cup has been reported to occur early in the clinical course of manifest

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glaucoma and in general to parallel the magnitude of field defects (Armaly 19 0) As a result a large cup is taken to indicate a suspicion of glaucoma and the usefulness of ophthalmoscopy in early detection of glaucoma has been repeatedly emphasized (Hollows & Graham 1966 Armaly 19/0 Fisher et al 19 0 Miller 19/2)

However there is also considerable overlapping of the distributions of cup sizes in normal and in glaucomatous eyes Some completely normal eyes have large cups while early glaucomatous visual field defects are encountered in eyes with small cup/disc ratios as well as in eyes with large cup/disc ratios (Armaly 196 Krakau 19/1 Holm et al 19/2)

Several studies have recently been devoted to a search for criteria other than cup size, which will help to differentiate between a physiological cup in the normal eye and a pathological excavation in glaucoma Using the characteristics of the optic nerve head in glaucoma as a starting point workers in this field have called renewed attention to disc pallor (Schwarz et al 19 3) small vessel count (Veith & Sacks 19/3) peripapillary halo (Primrose 1971) vertical ovalness (Kirsch & Andersson 19/3) and asymmetry (Fishman 19/0 Portney 197э) We must admit however that present methods of observin the disc do not reveal the early features of glaucomatous damage (Gloster & Parry 19/4)

Our ability to discern an acquired excavation on a certain occasion is dependent on our knowledge of the previous size of the cup in question Records of pertinent disc parameters however will continue to be desirable and utopian An alternative is to look for sources of variation in size of cups in normal eyes By taking such factors into account we could calculate expected (corrected) cup sizes with a narrower distribution which ought to facilitate the detection – not only of a glaucomatous excavation – but of any kind of pathological enlargement or diminution of the optic cup whether it is acquired or congenital

During the preparation of a report on the resemblance between tonometer readings on relatives and spouses we searched our entire material for a parameter that contrasted with the ocular tension by being to a great extent genetically determined Thus we found – like Nakajima (1961) before us – that the heredıtability of the disc diameter was high It immediately occurred to us that the heredity of the cup/disc ratio might result from a genetic determination of the disc diameter If so the cup size would depend on the size of the disc – a possibility earlier suspected by Tomlinsson and Phillips (1969 19/4) but otherwise effectively concealed by the common belief that the disc diameter is a constant and by the almost universal use of the cup/disc ratio to describe the size of cups

It was soon quite evident both from fundus photographs and from direct observations on patients that the sizes of cups and discs covaried Discs without

cups are usually perceptibly small while large discs often have remarkably large cups

The present study was undertaken in order to evaluate and if possible extend and substantiate this observation

After the submission of this report our attention has been drawn to a paper read before the American Ophthalmological Society and pointing out the covariation of cup and disc areas in 32 normal eyes (Teal et al 1972)

Material

The material was derived from a general ophthalmic population survey which was carried out at the Dalby Health Centre in southern Sweden from March 1969 to April 1970 Invitations with a brief questionnaire were mailed in rotation following a directory to all persons aged 8 years or more who had been resident in the village surrounding the Health Centre since December 1968 Out of 1 917 persons invited 1 70[illegible] (88 8 %) took part in the study Information about persons who failed to turn up has been given in an earlier report (Bengtsson 1972)

Fundus photography unlike other parts of the examination was frequently rendered difficult – most often by lens opacities or unsatisfactory cooperation in elderly persons A pair of photographs (one slide from each eye) was filed in 1 690 cases but reliable measurements of disc and cup size were obtained from no more than 2 334 phakic eyes in 1 322 cases – from both eyes in 1 012 cases from the right eye only in 118 cases

Table I
Age and sex composition of the material

Age (years)	Men	Women
8– 9	42	35
10–19	128	122
20–29	111	132
30–39	135	148
40–49	99	97
50–59	72	74
60–69	52	47
70–79	12	14
80–89	–	2
All ages	651	671

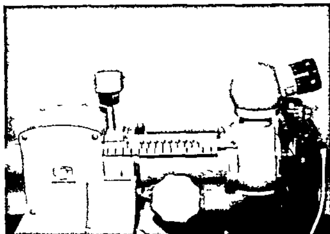


Fig 1
Slide rule used to facilitate focusing of the fundus camera

and from the left eye only in 199 cases Four patients with suspected or manifest glaucoma were excluded from parts of the investigation intended to describe normal conditions

Age and sex distributions are given in Table I

Methods

Determination of the visual acuity ophthalmometry slit lamp examination Goldmann tonometry Schiotz tonometry sphygmomanometric measurements of the systemic blood pressure ophthalmoscopy in mydriasis subjective refraction in cycloplegia and fundus photography were attempted in every case. Conventional equipment was used according to a fixed programme All data were recorded on special forms Transfer to punch cards and further processing were performed at the Computer Centre in Lund

Photographs were taken by a nurse using the West German Zeiss fundus camera with standard magnification and Kodachrome II film for colour transparencies (24 x 36 mm) A point half way between the disc and macula lutea was centred in the field of the photograph Focusing was greatly facilitated by the slide rule reproduced in Fig 1 This simple device enabled us to exploit the fact that the amount of extension (or telescoping) of the camera needed to ensure sharp pictures is directly proportional to the axial refraction of the eye examined The astigmatism correcting device of the camera was not used

The precautionary measure of taking no more and no less than two pictures of one individual photographing a check number twice in the middle of the film foll keeping a successive record of identity numbers and finally ordinary processing (resulting in boxes containing 36 paper slides numbered in series) secured identification with a reasonable expenditure of film and time

Horizontal and vertical diameters of cup and disc were measured as follows

In a preliminary study the elimination of bias was considered most essential We therefore deliberately selected an examiner unable to recognize changes associated with e g ageing or myopia The slides were enlarged on white paper at a fixed magnification (about 8×) and measurements taken with a millimeter rule by a technical assistant

It was considered likely however that the disc margin would be more accurately identified by a person with some clinical experience All slides were therefore projected on to a screen at a fixed magnification (about 16×) and remeasured on ruled paper by the author This time the distance between two scale divisions was two millimeters

When estimating the extent of cupping not only differences in colour between the cup and the rim but also other features such as deflections of vessels were taken into account The estimate was often easy as e g in the presence of an obvious edge to a deep cup or in the complete absence of cupping In other cases however the area of cupping had to be judged mainly from the colour difference Even in such cases the observer usually felt reasonably certain about the position of the circumference of the cup – provided that the picture was sharp (In normal eyes the area of cupping and pallor closely correspond – Schwartz 1973) In older people lenses undergoing nuclear sclerosis incompletely dilated pupils and insufficient cooperation often resulted in disturbances from reflected light reduced colour contrast and blurred pictures In the preliminary study measurements were attempted in spite of those difficulties After re structuring of the investigation however increased importance was attached to

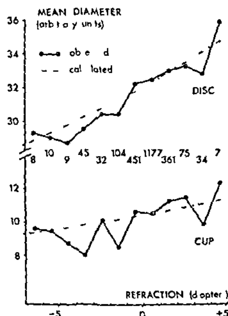


Fig 2

The effect of refraction on magnification The number of observations in each class is indicated

accuracy and precision Defects seriously impairing the reliability of measurements were no longer ignored and about 400 slides therefore were excluded from the present material.

The correlation between measurements (of the horizontal diameter) on the same slide *on two different occasions (a few weeks apart)* was thus increased from 0 87 (in the preliminary study) to 0 93 for the disc and from 0 95 to 0 98 for the cup (The distributions of cup and disc diameters differ a great deal and their repeatabilities are therefore not comparable)

The photographs were measured in the same order as they were taken The measurements were expressed in arbitrary units (approximately equivalent to 0 05 mm) The geometrical mean of the vertical and horizontal diameters was used to describe the size of the disc *or the cup of one eye except in 36 eyes in which the vertical diameter* of the disc had to do since the most nasal part of the optic nerve head was missing in the picture (Centering affects magnification to some extent but this error was not considered to have any serious or systematic effect on our results)

Results

I The effect of refraction on magnification

The linear magnification of a fundus photograph is dependent on the refraction of the eye examined but is not affected by the focusing (extension or telescoping) or positioning *(relative to the patient)* of the Zeiss camera (Behrendt & Doyle 1965) From the optical properties of this instrument as indicated by the directions for its use we expected the magnification G in a certain case to be related to the glass refraction D (in diopters) of the eye examined by the expression

$$\frac{G}{g} = \frac{1}{1-Df}$$

– in which g is the magnification when the eye examined is emmetropic and in which 1/f is the (normal) refractive power (in diopters) of the ocular media. When the value of f given by Gullstrand in his exact schematic eye (0 01,055 m) was put into this formula we obtained excellent agreement with a list of magnifications in nine points – from +12.57 D (3 10x) over 0 00 D (2 43x) to – 2? 0 D (1 79x) – courteously specified by the manufacturer A comprehensive derivation of the formula will be published shortly (Bengtsson & Krakau in manuscript)

In the present material the changes in cup and disc diameters with the best sphere refraction coincided to a great extent with the expected effect of refraction on magnification (Fig 2) We therefore decided to multiply all diameters by the factor (1–0 017055 D) in which D represents the glass refraction of the pertinent eye

Below all measurements are given in corrected length units which are uninfluenced by the effect of refraction on magnification

As expected the correction resulted in a decreased variance of cup and disc diameters as well as in an increased correlation between them To avoid misunderstanding we have found it necessary to point out that these effects were no more than marginal Contrary to our first assumption the effectiveness of correction for variations in magnification therefore seems to be of little consequence to our results in the present case

Table II

Covariation of cup and disc diameters (number of eyes with indicated measures)

CORRECTED AND ROUNDED CUP DIAMETER (ARBITRARY UNITS)

	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
32																							1			
31																										
30																										
29																										
28																							1			
27																						2				
26																			1		2					1
25																			1	2	1	1		1		
24													1			1	1	1	4		1					1
23														1	1	2	2	5	4		2					
22											1			1	1	3	4	2	2	3	2	1				
21													1	1	3	2	5	2	6	4	2	2				
20													1	6	3	5	5	3	3	2	2					1
19												2	2	11	6	6	12	3	8	2	1					
18									1	2	3	6	6	10	11	10	11	6	2							
17									2	3	2	6	12	15	14	17	5	1	1	1						
16										1	9	12	15	12	8	5	7	3								
15									3	7	12	26	26	21	17	4	7	2	1							
14									2	9	23	21	20	14	15	14	4	1								
13								4	7	16	28	30	27	23	7	3	3	1				1				
12							4	6	14	23	46	46	31	11	9	5	2				1					
11							5	8	11	31	31	41	20	9	7	4	1									
10						4	7	22	25	27	33	24	18	13	4	3										
9				1	2	2	11	26	40	49	50	23	11	7	2											
8					2	7	8	26	35	23	38	17	8	7	2						1					
7					3	7	16	23	26	23	27	10	5	3												
6						6	12	23	31	21	11	3	1	1											1	
5	1			2	1	5	16	20	12	9	7			1	1											
4					1	9	4	8	3		4			1												
3				3	4	3	7	2		2	3															
2		4	3	4	21	40	58	34	26	6	10	2	2	1												

CORRECTED AND ROUNDED DISC DIAMETER (ARBITRARY UNITS)

II. The variation of cup and disc diameters

?03 (9 %) of the discs had no cup at all Very small cups were however an infrequent finding and not one cup had a diameter of less than two units The major retinal vessels always occupied an area with a diameter of at least two units which of course was included in any existing cup but often irregular and difficult to measure in the absence of a cup We therefore decided to consider the vessels equivalent to a cup with a diameter of two units in otherwise un excavated discs

In spite of this step the distribution of cup diameters remained bimodal The major part was positively skewed and the range 2 to 32 units Cups much larger than the average one were common and there was a small but definite over lapping between the distributions of cup and disc diameters (Fig 3)

The distribution of disc diameters was positively skewed ($g_1 = 0.55$) with a mean of 32.3 a standard deviation of 3 4 and a range from 22 to 47 arbitrary units (Fig 3) (g_1 = Fisher s measure of skewness $= \frac{m_3}{s^3}$ m_3 is the third moment about the mean and s is the standard deviation)

III The covariation of cup and disc diameters

A simple cross table (Table II) alone revealed that the sizes of cups and discs covaried to a surprisingly great extent (r = 0 8) The mean cup diameter in creased from about 4 units – in discs with a diameter of 25 units – to 22 units –

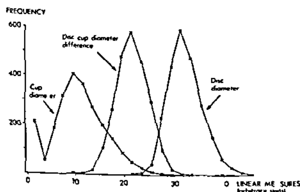


Fig 3
Frequency distributions of cup diameter disc diameter and disc cup diameter difference

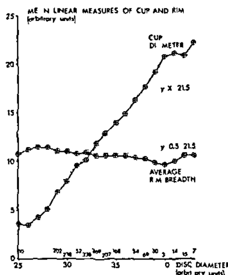


Fig 4

Change in cup diameter and average rim breadth with disc diameter The number of observations in each class is indicated Broken lines with characteristics indicated were included for comparison with the regression lines

in discs with a diameter of 43 units This increase was roughly linear and the slope of the regression curve came close to unity (Fig 4) As a first approximation the dependence of cup size on disc size might therefore be described by the simple statement that changes in cup diameter more or less parallelled those in disc diameter or equivalently that cup and disc diameters covaried in a way that left their difference largely unaffected by changes in disc size

IV The variation of "disc cup diameter differences" and "average rim breadths"

From a mathematical point of view the disc cup diameter difference (d–c) provides the most obvious linear measure of the amount of tissue in the optic nerve head – and for comparison with the dispersion of disc and cup diameters the disc cup diameter difference was considered irreplaceable For other purposes however we preferred to use the average rim breadth $(\frac{d-c}{2})$ since we expected it to be more easily understood

The disc cup diameter difference had a mean of 21 6 a standard deviation of 3 2 and (one observation disregarded) a range from 10 to 34 units In other

words disc cup diameter differences were much less dispersed than cup diameters and (in absolute numbers) also somewhat less dispersed than disc diameters (Fig 3)

Average rim breadths were largely independent of disc size (Fig 4) and their distribution was very nearly normal (Fig 5)

In short linear measures of the amount of tissue in the optic nerve head were independent of disc size normally distributed much less dispersed than cup diameters and somewhat less dispersed than disc diameters

V The average rim breadth in eyes with signs of previous posterior uveitis

The original records were searched for common characteristics of persons with extremely large or small disc diameters or rim breadths No obvious characteris tic associated with aberrant disc size was found Twelve cases had an average rim breadth smaller than 6 75 units Not less than five of them had signs of a previous posterior uveitis We therefore compared the distributions of the average rim breadth in eyes with and without a note of such signs

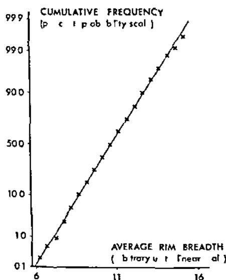


Fig 5
Plot on probability paper showing that the average rim breadths were very nearly normally distributed

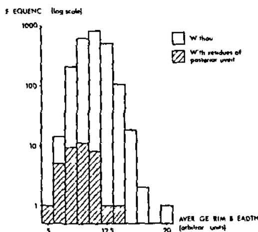


Fig 6

I requency distributions of average rim breadths in eyes with and without signs of previous posterior uveitis

A special coding system had been prepared in advance and was used through out the survey In order to avoid bias we selected all eyes to which had been assigned at least one of three pertinent code numbers signifying

1 Scars in retina and choroid

2 Scars in retina choroid and vitreous

3 Vitreous opacities not associated with vitreous detachment and not caused by lipid depositions

Fig 6 shows that the distribution of average rim breadths was displaced to the left (towards lower values) in 36 eyes with residues of posterior uveitis when compared with its counterpart in other "normal eyes The difference between the two means was highly significant (Student s $t = 6\ 6$) and a recheck made it clear that this finding was not caused by a misinterpretation of e g an increased pallor of postuveitic nerve heads On the contrary the position of the circum ference of the cup was never in dispute

A notable fact was that among several deep cups with sharp edges deflected vessels and small rim breadths in this group not one aroused a suspicion of glaucoma in the original survey (This illustrates that if the cup is initially small a moderate increase in size may not attract attention – whereas a large cup is likely to arouse suspicion whether it is glaucomatous or not)

VI. Possible association between broad rims and squints

Among 58 persons with an average rim breadth" of 14 units (mean + 2 SD) or more in at least one eye five pairs of first degree relatives attracted our attention In two of them one member squinted In two additional cases a third member of the family squinted Their discs had been difficult to measure but were found to have very broad rims when re checked The fifth pair consisted of two brothers whose mother squinted Her average rim breadth was more ordinary (11 units) but remarkably enough brought into line by a retino choroidal scar in one of the eyes The statistical significance of this finding is of course not easily tested but we felt compelled to suspect a genetic association between broad rims and certain squints Squinting persons in general however had standard rim breadths

Discussion

The use of the disc diameter as a measure of fundus lesions and likewise the use of the cup disc ratio (c/d) to describe the size of the optic cup are based on the assumption that the disc diameter is practically constant Once more or less universally accepted these criteria have rendered absolute measurements superfluous and thereby effectively concealed the obvious fact that the size of the optic nerve head is subject to continuous biological variation Even advocates of more accurate methods give e g the calibre of retinal vessels in fractions of the disc diameter Hypoplasia of the optic nerve and Megalopapilla are regarded as exceptions proving the rule and are generally described as having a disc size distinctly and discretely different from the normal

On second thoughts we did of course expect the discs to vary in size and were not surprised to find that our values for the mean and standard deviation of disc diameters (32 3 ± 3 4 units equal to about 0 05 mm) agreed with those reported by Franceshetti & Bock (1950) (1 62 ± 0 15 mm) The distribution was continuous and unimodal Very large (or small) discs are surely inherited and very likely congenital but not necessarily anomalous and hardly worthy of a special term such as Megalopapilla unless otherwise qualified

The coefficient of variation for disc diameters is not subordinate to that for body length of adults Nobody would dream of giving a measurement in units of individual body length or fractions thereof Similarly the use of the disc diameter as a measure of fundus structures should be abandoned One alternative proved feasible in the present study Several others have been described earlier (Bretagne 1926 Morgan 1927 Franceshetti & Bock 1950 Holm & Krakau 1969)

In our material some apparently quite normal discs had an area more than four times larger than that of other equally normal ones The variations in disc diameter were however in general parallelled by similar variations in cup diameter The amount of tissue in the optic nerve head therefore varied somewhat less than the disc size

The existence of a fixed number of nerve fibres with standard cross sections and a suitable amount of glia proportioned to them would cause the *area* of the tissue in the optic nerve head to remain unaffected by variations in cup and disc sizes The rim *breadth* on the other hand would remain constant if e g tissue support was limited by the distance to the disc margin In both cases variation in cup size might originate within the cup itself (caused by e g differently sized Bergmeister s papillas) or be secondary to changes in disc size The cup diameter would be related to the disc diameter by the expressions $c = \sqrt{d - a^2}$ (in which a is the diameter in a circle with the same area as the disc tissue and accordingly presumed to be constant) and c = d °b (in which b is the average rim breadth and accordingly presumed to be constant) respectively A comparison between observed data and curves with such characteristics gave no conclusive evidence enabling us to fix on one of the two hypotheses

Generalisations based on the shape position and slope of regression curves are liable to serious errors For the main purpose of the present study – which is purely descriptive – information derived from Figs 3 and 4 can however be used with confidence Our statement that cup diameters were unevenly distributed and heavily dependent on disc diameters while "average rim bre dths were normally distributed much less dispersed than cup diameters and independent of disc sizes was considered to give an adequate description of th main findings in the present study A multiple regression analysis of the pre t material will be published shortly

m parison between the dispersions of cup/disc ratios and disc cup diameter rences has to be made in an indirect way since the two variables have different d nsions We therefore multiplied the cup/disc ratio by the mean disc diameter (M_d) Thus we found the dispersion of cup/disc ratios to be intermediate – var($\frac{cM_d}{}$) = 17 0 – between the dispersion of cup diameters – var c 26 0 – and that of meter differences – var (d–c) = var 2b = 10 2 – when all three variables the same units

The connection with other findings in the present study is evi

The variance of a ratio between two variables (X_1 and X) of the variance and means (M_1 and M) of the original va tion –

$$\mathrm{var}\,(X_1/X\ ) = \frac{M_1}{M_2^2}\ (\ \frac{\mathrm{var}\,X_1}{M_1} - \frac{2\,\mathrm{cov}\,(X_1\ X\ )}{M_1 M_} + \ \mathrm{va}$$

– provided that the standard deviations are small compar

$$\text{var}\frac{cM_d}{d} = M_d^2 \ \text{var}\,(c/d) = \text{var}\,c - \frac{2M_c}{M_d}\,\text{cov}\,(c\,d) + \frac{M_c^2}{M_d^2}\,\text{var}\ d$$

in which the last term is small in comparison with the others and can be neglected for the present purpose ($M_c = 10\ 7$ cov (c d) = 13 9) In other words The covariation of cup and disc diameters renders cup/disc ratios less dispersed than cup diameters

Similarly since

$$\text{var}\,(c/d) = \text{var}\frac{d-2b}{d} = \text{var}\,(1-2b/d) = \text{var}\,1 + \text{var}\,(2b\ d) = \text{var}\,(2b/d)$$

we also have

$$\text{var}\frac{cM_d}{d} = M_d^2\ \text{var}\,(2b/d) = \text{var}\,2b - \frac{2M_{2b}}{M_d}\,\text{cov}\,(2b\ d) + \frac{M_{2b}^2}{M_d^2}\,\text{var}\ d$$

in which the covariance term can be neglected since b and d are independent of each other In other words The variation of disc diameters causes the cup/disc ratio to be more dispersed than disc cup diameter differences

The question whether the use of the average rim breadth to replace the cup disc ratio would improve the early diagnosis of glaucoma or papilloedema could of course not be answered in the present study We feel however that by taking the covariation of cup and disc diameters into account the detection of any enlargement or diminution of the optic cup ought to be facilitated The association of uveitis and squints with aberrant rim breadths in the present material seems to lend an air of credibility to such expectations

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PERIPHERAL VISUAL FIELD RESTRICTION IN CHLOROQUINE RETINOPATHY

Report of a Case

BY

MARTIN LOWES

Chloroquine compounds are known to cause a retinopathy which typically begins in the central fundus giving rise to a bull s eye macula Ultimately peripheral changes may become apparent In the routine eye examination of such patients emphasis has been laid on the central area of the fundus A case is presented where the retinopathy was not diagnosed until marked peripheral changes had occurred with peripheral pigment changes at tenuated retinal vessels slight optic atrophy peripheral visual field re striction and a subnormal electroretinogram The typical bull s eye changes were not apparent Routine examination of the peripheral fundus by means of ophthalmoscopy and perimetry is necessary to avoid missing any such retinopathy

Key words chloroquine – resochin retinopathy – peripheral retina – ophthalmoscopy – perimetry – visual field restriction – electroretinography

Chloroquine was originally synthesised for use as an antimalarial agent Page (1951) introduced mepacrine in the treatment of lupus erythematosus and since then the synthetic antimalarial compounds have had an important role in the

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treatment of a variety of collagenoses and skin diseases The dosage usually from 250–750 mg daily over a period of months to years is many times in excess of that given for the short antimalarial course Such long term treatment can cause a characteristic retinopathy giving rise to a severe and permanent visual handicap The retinotoxic effects were described by Hobbs et al (1959) and have since been well documented by Nylander (1967) In spite of stopping the treatment the retinopathy may progress due to the pronounced accumulative properties of the drug in the melanin containing tissues of the eye (Rubin et al 1963)

The serious retinotoxic effects have led to the necessity of continuous ophthalmological control during chloroquine treatment As far as the detection of the retinopathy is concerned the emphasis has been laid on the central area of the fundus (Okun et al 1963 Henkind et al 1964 Carr et al 1966 Percival & Behrman 1969) The present case illustrates that marked peripheral changes may occur before the characteristic central changes and stresses the necessity of evaluating the periphery of the fundus as well as the macula in patients treated with long term doses of chloroquine compounds

Case Report

A 71 year old woman developed joint symptoms in March 1967 consistent with a diagnosis of rheumatoid arthritis Treatment with a chloroquine compound (Resochin) was commenced in April 1971 because of a continued and considerable activity of the arthritis A daily dose of 500 mg controlled the condition and was maintained until May 19[illegible] The treatment was continuous except for 10 days in July 1971 and a 3 month period from May to July 1973 which caused a relapse A total chloroquine dosage in the region of 700 g was given Ophthalmological examination was performed regularly throughout the course of treatment The patient was seen prior to treatment and a total of nine eye examinations were performed up to the time of diagnosis of the retinopathy

The patient began to experience fainting attacks in May 1975 and noted a defect in the upper outer field of vision of the right eye She was admitted to a general medical ward and an eye examination was requested because of a suspected intra cerebral tumour

Eye examination May 1975

Visual acuity was 1 0 right eye and 1 0 left eye Colour vision with Ishihara plates was normal Slit lamp examination revealed several thin linear corneal opacities which had originally been observed 9 months previously

Ophthalmoscopy showed slight bilateral optic nerve atrophy with the right optic disc paler than the left There was a marked narrowing of the retinal arterioles especially involving the lower nasal branches Peripherally from the equator outwards numerous small round and regular pigment aggregations were seen These findings had not been described in the previous examinations A few small pigment epithelium defects were

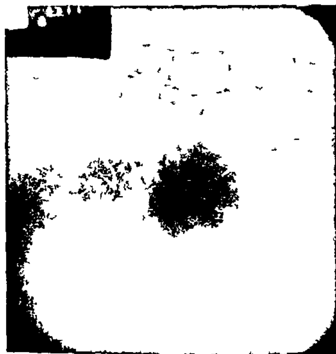


Fig 1
Fluorescein angiography of right macula showing discrete pigment epithelium defects (36 seconds)

just visible in the region of the right macula The left macula appeared quite normal There were no characteristic bull's eye changes and no central pigment deposits Fluorescein angiography of the right eye revealed a few small slightly confluent pigment epithelium defects in the macula area but no bull's eye pattern (Fig 1) There was an increase in the peripheral background choroidal flourescence with pigment aggregations (Fig 2) Visual field examination with the Goldmann perimeter revealed restriction of the peripheral fields especially involving the upper temporal quadrants No definite scotomas could be elicited (Fig 3a)

Electroretinography showed a subnormal but positive curve Dark adaptation revealed a normal biphasic curve.

A diagnosis of chloroquine retinopathy was made and treatment was immediatedly stopped

Eye examination October 1975

Visual acuity was 1 0 right eye, and 0 67 left eye Colour vision was normal Slit lamp examination showed almost complete disappearance of the corneal deposits

Ophthalmoscopy was unchanged the right macula remained unaltered and the left macula still appeared normal Fluorescein angiography of the right eye revealed a few



Fig 2
Fluorescein angiography of the peripheral retina of right eye showing increased background fluorescence and pigment aggregations (1.0 seconds)

more central pigment epithelium defects Fluorescein angiography of the left eye showed a normal macula without any sign of pigment epithelium defects

Visual field examination demonstrated increased peripheral field restriction with paracentral scotomas (Fig 3b) Electroretinography was of the negative (–) type

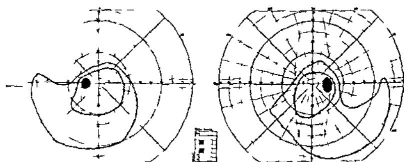


Fig 3a
Visual fields at the time of diagnosis of the retinopathy

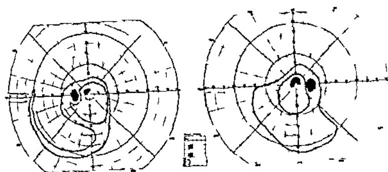


Fig 3b
Visual fields 6 months after stopping chloroquine treatment

Eye examination January 1976

Visual fields (Fig 3c) showed some improvement with regression of the central scotomas

Electroretinography was again positive but still subnormal Moreover the patient s hair which had become bleached under the chloroquine treatment had begun to return to its usual brown colour

Eye examination August 1976

Visual acuity and colour vision were normal Ophthalmoscopy was unchanged The retinal vessel attenuation optic atrophy and peripheral pigmentation were unaltered There was no bull s eye pattern or pigment deposition in the central fundus

Visual fields showed disappearance of the paracentral scotomas for 1/4 objects but otherwise largely unchanged peripheral field constriction (Fig 3d)

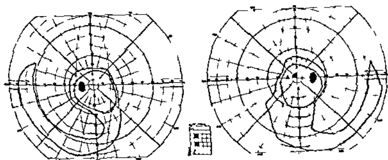


Fig 3c
Visual fields 9 months after stopping chloroquine treatment

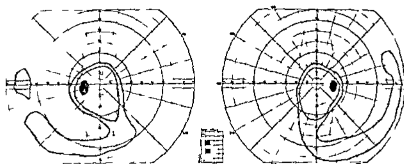


Fig 3d
Visual fields 16 months after stopping chloroquine treatment

Discussion

In the case described a retinopathy developed in spite of regular ophthalmological control The retinopathy was however uncharacteristic in that there was marked peripheral involvement without any bull s eye pattern in the central fundus Visual field examination revealed peripheral constriction Central scotomas were not found at the time of diagnosis of the retinopathy The visual field defects were first noted by the patient in connection with fainting attacks when admission to a medical ward led to examination of the entire visual fields and a diagnosis of chloroquine retinopathy Follow up of the patient has been carried out for 16 months and no definite bull s eye changes have become apparent whereas the visual field constriction has largely remained unchanged

It is widely accepted that in chloroquine retinopathy the first changes occur in the central fundus After describing some of the first cases of chloroquine retinopathy Hobbs et al (1959) were of the opinion that the retinopathy began with narrowing of the arterioles and retinal oedema and later progressed to pigmentation both peripherally and centrally However Okun et al (1963) found that pericentral scotoma was an early and constant feature and that as the retinopathy progressed the peripheral field became constricted with extension of the scotoma They maintained that the earliest fundus changes occur in the macula and that these are followed by narrowing of the retinal vessels Peripheral pigment changes were described as being a very late phenomenon

In a discussion concerning the early retinal changes Henkind et al (1964) observed that macular mottling was the first visible sign of chloroquine retino-

pathy and only one out of 14 patients with early retinopathy showed visible arteriolar narrowing

Crews (1969) has graded patients according to their fundus appearance on ophthalmoscopy Grade 1 normal macula and fovea grade 2 foveal reflex absent grade 3 perifoveal pigmentation grade 4 depigmentation grade 5 bull s eye macula grade 6 optic atrophy and narrowed arterioles Reliable scotoma could only be detected in grades 3–6 In the most advanced grade (6) peripheral constriction was also present Carr et al (1966) observed that although the earliest ophthalmoscopical changes were in the macula area retinal profiles to red light indicated that some damage also occurs at the periphery They felt however that in the early stages central damage is more severe than peripheral damage

Nylander (1967) found in a number of cases of slight retinopathy that a subnormal ERG was the first evidence in support of the diagnosis The macula changes were then so discrete that they were not evaluated as pathological He concluded that in certain cases it appeared that some involvement of the rods in the periphery could occur before any conspicuous macular lesions were demonstrable

In the present case ophthalmoscopy perimetry and ERG examination revealed marked involvement of the peripheral fundus with pigment changes narrowed arterioles and slight optic nerve atrophy Fluorescein angiography showed minimal changes in the macula area with only a few pigment epithelium defects The typical fluorescein angiography pattern with bull s eye macula have been described by Kearns & Hollenhorst (1966) The ERG was interesting in that it was originally positive but subnormal progressing to a negative (–) type before again reverting to a positive curve implying some recovery of rod function The normal dark adaptation curve is in agreement with other authors (Okun et al 1963 Henkind et al 1964 Carr et al 1966) who have similarly found normal or only slightly reduced rod thresholds even in relatively advanced cases of chloroquine retinopathy

The present case demonstrates that by concentrating on the central fundus only there is a very real danger of missing the retinopathy A normal central fundus may give a sense of false security Practically it is therefore important to routinely examine the peripheral fundus by means of ophthalmoscopy and perimetry in patients undergoing long term treatment with chloroquine preparations As regards the frequency of these control examinations the patients need not be seen more than once during the first year of treatment but should be examined more frequently as the total dose increases and exceeds 300 g (Nylander 1967)

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TEMPORAL LOBE EPILEPSY AND NEURO OPHTHALMOLOGY

Ophthalmological Findings in 74 Temporal Lobe Resected Patients

BY

INGE JENSEN and H H SEEDORFF

A survey is presented of the ophthalmological findings in 74 patients with drug resistant temporal lobe epilepsy who underwent unilateral anterior temporal lobectomy 1960–1969 at Rigshospitalet, Copenhagen. At follow up 1970–1971 one to ten years following the operation 81% of the patients had no or only few seizures The visual acuity remained unchanged in all patients following the operation. Preoperatively a visual field defect was observed in 2 patients At follow up 51 patients had homonymous hemianopias in 38 of them this was limited to the upper quadrants and in 13 patients also included the lower quadrants but was characterized as a total homonymous hemianopia in only 6 patients The presence and extent of the visual field defects were correlated to surgical results age at onset of epilepsy age at operation preoperative duration of epilepsy presence of grand mal preoperative complications and neuropathological findings but without observing any statistically significant conclusions On the other hand the extent of the postoperative visual field defect was significantly influenced by the side of the operation, with more and larger defects following right sided lobectomies In the 51 patients with postoperative hemianopias this defect was either unobserved by the patient or regarded as a considerably less important handicap than the frequent and socially invalidating preoperative seizures

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Preoperatively 11 % of the patients had suffered from strabismus as compared to an expected frequency of 5 % but this trend just falls short of statistical significance

Key words temporal lobe epilepsy – temporal lobe resection – visual acuity – visual field defect – congruity – macular involvement – strabismus

Unilateral anterior temporal lobectomy has since 1948 proved to be an excellent form of treatment for drug resistant temporal lobe epilepsy of unilateral or predominantly unilateral origin To date surveys covering more than 2000 operations have been published (Inge Jensen 1975a Van Buren et al 1975) In summary the outcome is that two thirds of the patients at follow up one to ten years after the operation had no or only few seizures and in more than three quarters of the patients the operation could be described as worth while Furthermore over half of the patients who preoperatively had displayed some psychiatric disorders were normalized or had markedly improved

Homonymous hemianopic visual field defects were found to be frequent sequelae of this operation (Guillaume & Mazard 1956 Brown et al 1956 Bailey 1954 Falconer & Wilson 1958 Van Buren & Baldwin 1958 Walker & Walsh 1958 Falconer & Serafetinides 1963 Davis 1963 Green & Scheetz 1964 Hullay 1965 Green 1967 Marino & Rasmussen 1968) The study of these visual field defects has contributed to the elucidation of the anatomy of the visual pathways in the temporal region of the brain Previously the knowledge of the visual pathways was largely based on visual field defects observed in patients with tumours (e g Cushing 1922 Oldberg 1937 Edmund 1954) or with traumatic lesions especially gun shot wounds but in these patients the intracerebral lesion was seldom well defined In contrast to those lesions an anterior temporal lobectomy is a well defined lesion Investigations of the patients with such lesions have made it possible to verify the theories about the visual pathways in this area (Falconer & Wilson 1958 Van Buren & Baldwin 1958 Marino & Rasmussen 1968 Walker & Walsh 1968) These authors have correlated the visual field defects to the extent of the operation and the surgical results and thus tried to map out the visual pathways The present investigation cannot with regard to the visual pathways in any way supplement the information furnished by these authors We have tried to present a compiled analysis of the ophthalmological status preoperatively and at follow up the purpose of the investigation being to correlate the ophthalmological findings to the surgical results and to other clinical aspects

The surgical treatment of drug resistant temporal lobe epilepsy was instituted in Denmark in 1960 and by the end of March 1975 a total of 106 patients had been submitted to an anterior temporal lobe resection (Inge Jensen & Vaernet 1976)

Operative method

The operation consisted of an anterior temporal lobectomy usually going back to the vein of Labbe the extent of the excision ranging from 5 5 to 7 cm Where no well defined vein of Labbe existed or where it ran posterior to this limit the excision was carried back to a point 6 cm from the temporal pole in the dominant hemisphere and 7 cm in the non dominant hemisphere The superior temporal gyrus apart from the anterior 2 cm was preserved in order to minimize the risk of postoperative dysphasia All operations but one were performed by Kjeld Vaernet who followed the principles laid down at the Guy s Maudsley Hospital by Falconer (Falconer et al 1955 Falconer 1965) resecting the tip of the temporal lobe including the mesial structures en bloc so that the whole specimen was available for histological examination.

Case material

The present material consists of the first 74 patients with drug resistant temporal lobe epilepsy who during the period 1960–1969 were treated with unilateral temporal lobe resection of University Clinic of Neurosurgery Rigshospitalet Copenhagen Neither before nor during the operation was any tumour or gross vascular malformation recognized in any of the patients All patients suffered from psychomotor and/or focal eizures originating from the temporal lobe and 55 of them also had grand mal Their epilepsy was extremely severe and preoperatively all of them were socially handicapped due to their frequent and severe seizures and/or psychiatric disturbances In all patients a unilateral or predominantly unilateral spike discharging temporal focus was demonstrated in routine EEG scalp recordings with sleep recordings or recordings with sphenoidal electrodes

The material comprises 43 males and 31 females At the time of the operation the ages of the patients ranged from 4–54 years with 14 of them being 15 years or younger The median follow up period was 5 1 years In 60 of the patients the pre operative duration of epilepsy was more than 4 years

A retrospective follow up investigation was undertaken in 1970–1971 covering various clinical genetical aetiological social psychological neuropathological and electroencephalographic aspects Some of these results have been already published (Inge Jensen 1975a b c 19 6a b Inge Jensen & Klinken 1976 Inge Jensen & Vaernet 1976) The overall effect of the operation on the seizures was found to be that 61 % of the patients were free from any seizures 20 % had obtained a reduction in their seizure frequency by at least 75 % while the remaining 19 % belong to the group no change which comprises some reduction in seizure frequency no change and the four postoperative deaths (Table I) Table I also indicates that a unilateral temporal lobectomy favourably influences the psychiatric status as one third of the patients were found to be without any psychiatric abnormality at the follow up investigation as compared to one eighth at the time of the operation, and further that another third showed marked psychiatric improvement

Table I
Effect of temporal lobe resection on seizures versus psychiatric status at follow up

	No seizures	Marked reduction	Some reduction	No change	Death	Total
Psychiatric status						
Normal						
(pre and postop)	4	2	0	0	0	6 8%
(only postop	11	4	0	1	0	16 22%
Abnormal						
Markedly improved	13	5	1	1	0	20 27%
Improved	3	1	1	0	0	5 7%
Unchanged/deteriorated						
(abnormal preop)	11	3	2	2	4	22 30%
(normal preop)	3	0	1	1	0	3 [illegible]%
Total	45 61%	15 20%	5 7%	4 5%	4 5%	74 100%

As previously stated this investigation is retrospective but all patients provided they could cooperate were routinely examined immediately prior to the operation and one week postoperatively at the University Clinic of Neuro ophthalmology Rigshospitalet It can further be noted that these 74 patients prior to the operation were examined by ophthalmologists on a total of at least 343 occasions during their hospital admissions and on a further 245 occasions postoperatively not including the examination at the follow up in ation which was also performed at the University Clinic of Neuro ophthalmology Rigshospitalet

The neuro ophthalmological examinations generally included

1) visual acuity
2) eye position and eye movements and pupillary conditions
3) ophthalmoscopy
4) visual field examination by campimetry (Bjerrum)

and these examinations were if necessary supplemented with others

At the follow up investigation 1970–71 all 70 surviving patients were examined clinically Due to various irrelevant causes the ophthalmological examinations were not carried out in four patients (Nos 16 18 46 and 62) The visual field has post

operatively been recorded as normal in two of these (Nos 18 and 62) in one (No 16) a total homonymous hemianopia was recorded postoperatively a defect which was still present and inconvenient to the patient the last of these patients (No 46) an autistic and imbecile boy could not cooperate but reacted normally to threats from various visual angles Two of the four deceased patients were never *examined post* operatively (Nos 4 and 6) one (No 35) had had normal postoperative examinations while in the last patient (No 32) a right sided homonymous anopia affecting the *upper quadrants had been described The neuro ophthalmological case material in*cludes a total of 69 patients (Table II)

Results of Neuro Ophthalmological Examinations

Visual acuity

At follow up all patients were found to possess the same visual acuity as preoperatively

Table II

Visual field defects correlated to side of operation The details are referring to the 69 patients available for examination

	Side of operation		Total N = 74
	right N = 39	left N = 35	
No visual field defect	11	7	18
Visual field defect present	26	25	51
No examination	2	3	5[1]
Extent of visual field defect			
affecting only upper quadrants	15	23	38
partly including lower quadrants	6	1	7
total hemianopia	5	1	6
Congruity of visual field defects	15	14	29
Incongruity of visual field defects	11	9[2]	20
Macular involvement	8	3	11

[1] Cases Nos *4 6 32 35 and 46*

[2] 2 patients have been excluded (Case No 2 due to impaired cooperation Case No 5 due to choroidal tumour)

Visual field defects

Numerically and clinically the most important finding has been the post operative visual field defect which as a homonymous hemianopia of a vaying extent was present in 51 of the 69 patients examined Preoperatively homo nymous hemianopia was present in two patients (Nos 29 and 76), this was completely unchanged at follow up

While the occurrence of a postoperative hemianopia was independent of the side of the operation (Table II) 71 % in right sided temporal lobectomies and 73 % in left sided the extent of the anopia was significantly influenced by the side as the lower quadrants were affected in 11 patients (i e 29 %) operated upon the right side as compared to two patients (i e 6 %) operated upon the left In six patients the visual field defects were total hemianopias only one of these was operated on the left (No 16) The finding that the left sided anopias are more extensive is presumably due to the extent of the lobectomy which was generally greatest on the right side (Inge Jensen & Vaernet 1976) When calculating the extent of the visual field defects it was found that the left sided defects were approximately 30 % larger than the right si ed

The difficulties in recognizing whether the observed visual field defects are ...gruent or non congruent are mainly due to the fact that the horizontal borders can be difficult to define It is generally acknowledged that the ver ...l border is always sharp By contrast the horizontal border tends to be ...ping to a degree which varies according to the isopter used

The establishment of standards for congruity versus incongruity has been ...pted by Van Buren & Baldwin (1958) According to these authors con ... present when the difference between the extent of the visual field ... is less than 5° on repeated examinations Observing these standards ...und congruent visual field defects in 29 of the 49 patients with visual ...d defects at follow up (i e 59 %) a number which corresponds with the ... observed by Walker & Walsh (1968) in their 18 patients The question ... congruity versus non congruity of the visual field defects has also been investigated as shown in Table 2 without any positive conclusions being reached

In accordance with Falconer & Wilson (1958) Van Buren & Baldwin (1958) Marino & Rasmussen (1968) and Walker & Walsh (1968) we observed that with few exceptions the visual field defects were consistently most marked on the ipsilateral side with the difference on average amounting to 5 %

The vision was unchanged postoperatively in all patients but in eleven of them the visual field defect was found to be so centrally localized that in volvement of the macula must have occurred

It is worth noting that a visual field defect affecting the upper quadrant only is in most cases unnoticed by the patient and not revealed until the neuro ophthalmological examination as already observed by Rønne (1915). On the other hand a visual field defect involving the lower quadrants will severely inconvenience the patient and might for example prevent the patient from obtaining a driving license as was the case in 13 of the patients.

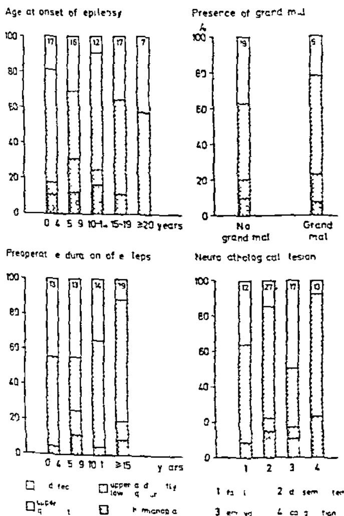


Fig. 1
The presence and extent of postoperative visual field defects correlated to various clinical variables

Table III

Visual field defects correlated to various variables (69 patients available for examination)

	Visual field defect			
	present N = 51		absent N = 18	
Surgical results				
no seizures	33	75 %	11	25 %
still seizures	18	72 %	7	28 %
Age at onset of epilepsy				
< 15 years	36	80 %	9	20 %
≧ 15 years	15	63 %	9	38 %
Age at operation				
≦ 15 years	7	54 %	6	46 %
> 15 years	44	79 %	12	21 %
Preoperative duration of epilepsy				
< 10 years	16	62 %	10	38 %
≧ 10 years	35	81 %	8	19 %
Grand mal				
present	39	78 %	11	22 %
absent	12	63 %	7	37 %
Peroperative complications				
present	8	89 %	1	11 %
absent	43	72 %	17	28 %
Neuropathology				
disseminated	23	85 %	4	15 %
focal	7	58 %	5	42 %
questionably abnormal	9	53 %	8	47 %
previous coagulation	12	92 %	1	8 %
Strabismus				
present	8	100 %	0	–
absent	43	70 %	18	30 %

The presence of a postoperative visual field defect has been correlated to various clinical aspects as shown in Fig 1 and Table III The presence or absence of a visual field defect does not in any way prognostically influence the surgical outcome regarding relief from seizures but with an increase in

the extent of the visual field defect an increase in the number of seizure free patients is observed No visual field defect – *61 %* seizure free patients a visual field defect involving the upper quadrants alone – 62 % seizure free patients and a visual field defect also involving the lower quadrants – 69 % seizure free patients This trend is however not statistically significant

Apparently it would seem that preoperative presence of grand mal seizures young age at onset of epilepsy a long preoperative duration of epilepsy and consequently higher age at operation peroperative difficulties with the haemo stasis and preoperative strabismus promote the occurrence of a postoperative visual field defect but these trends are not statistically significant

With regard to the neuropathological findings it is observed that the more *diffuse and disseminated the lesion the higher the incidence of visual field* defects

Strabismus

A total of eight patients (i e 10 8 %) had strabismus all of whom were sub mitted to operative correction This incidence was considerably highly than expected from the incidence in normal school children of 4.5 % (Anna D Frandsen 1960) but the difference is not statistically significant She also

Table II
The presence of strabismus correlated to various clinical variables

	Strabismus	
	present N = 8	absent N = 66
Surgical results		
no seizures	7	38
marked reduction	1	14
no change	0	14
Predisposition to neurological disease		
present	2	34
absent	6	32
Perinatal complication		
present	3	25
absent	5	41

found an increasing incidence of strabismus with decreasing intellectual levels Our findings are in full accordance with Millar (1965) who in his material of 401 patients with epilepsy observed an incidence of 10 % He concluded that the tendency to squint was more closely correlated to birth injuries than to the severity of the epilepsy This conclusion could not be substantiated by the pesent investigation

Apparently the presence of strabismus favourably influences the surgical prognosis regarding relief from seizures but this trend is definitely not statistically significant (Table IV)

Discussion

Wilbrand (1890) was one of the first to describe the architecture of the visual pathways and with regard to their course in the temporal lobe he stated that the visual pathways after their departure from the lateral geniculate bodies divide into three bundles a superior horizontal bundle comprising nerve fibres from the homonymous superior half of the retina an inferior one comprising nerve fibres from the inferior part of the homonymous half of the retina and lastly an intermediary bundle which is displaced somewhat medially and which contains nerve fibres from the corresponding homonymous macula areas Meyer (1907) was of the opinion that the inferior (ventral) nerve fibres after the departure from the lateral geniculate bodies bend forward and pass round and over the temporal horn of the lateral ventricle Meyer s loop before they continue backwards down into the inferior part of the temporal lobe and into the lateral wall of the lateral ventricle to join the two other bundles mentioned previously on their common path to the occipital lobe

Rønne (1915 1919 1938) in his concept of the visual pathways in the temporal lobe was in full agreement with the authors mentioned above He based his observations on clinical case histories and one of his conclusions was that a visual field defect in upper homonymous quadrants must be a symptom of a lesion in the temporal lobe affecting Meyer s loop As one of the first Rønne (1915) discussed the question of congruity versus non congruity in lesions in the temporal lobes

Rønne (1915) and Harrington (1939) among others advocated the concept that the course of the nerve fibres in the visual pathways in the temporal lobe is subject to extremely marked individual variations Rønne (1915) Traquair (1922 1949) and Falconer & Wilson (1958) were of the opinion that lesions in the temporal lobe generally result in congruity of the visual field defects and that the demarcation lines will as a rule be sharp In contrast Cushing

(19??) based on his own operative experience was of the opinion that in congruity is predominant following lesions in the temporal lobe due to the natomical fact that the homonymous nerve fibres had not yet joined each other Furthermore he was of the opinion that the horizontal inferior border of the visual field defect was always sloping

As previously mentioned the study of the visual field defects after well defined temporal lobe resections in drug resistant temporal lobe epilepsy has presented the best information to date concerning the architecture of the visual pathways Investigations by Van Buren & Baldwin (1958) and Walker & Walsh (1968) supported the concept that operative lesions in the temporal lobe generally result in incongruity of the visual field defects Walker & Walsh (1968) asserted that this point of view is supported by the results from studies on the retrograde degeneration of nerve cells in the lateral geniculate corpora following lesions in the optic radiation and the striate area respectively These studies would according to Walker & Walsh (1968) also account for the fact that the vertical demarcation of the visual field defect always is sharp while the horizontal tend to be sloping

Ronne (1915) was very interested in the difficulties in determining the horizontal border in visual field defects This difficulty is probably the main reason for the as yet unresolved divergences concerning the concept of congruity It is generally agreed that the vertical border is always sharp independent of the isopters used while on the other hand there can be considerable variations in the horizontal border This horizontal borderline zone might depending upon the isopters assume a fan like appearance which in incongruity might appear as a relative defect on one side and as an absolute defect on the other for the same object

The question of congruity versus incongruity is also a question of accepting a rigid and more and less arbitrary standard of 5° with regard to the horizontal borderline Like Walker & Walsh (1968) we are disinclined to accept a ruling that visual field defects should be considered congruent when a difference of 5° is accepted We therefore agree with Harrington (1939) and Walsh & Hoyt (1969) who conclude that the more posterior the localization of the lesion the more the visual field defects approach congruity becoming definitely congruent in lesions close to the striate area The reason for the incongruity or at any rate questionable congruity in lesions in the temporal lobe as compared to a definite congruity in lesions in the occipital lobe is that the corresponding nerve fibres from the homonymous retinae anatomically complete their fusion very close to the striate area

The presence or the extent of the visual field defects is largely dependent upon the extent of the operative lesion as demonstrated by Harrington (1961)

who observed that resections performed 8 cm or more from the tip of the temporal pole very frequently resulted in total hemianopia This complication might also be due to disturbances of the blood supply to the visual pathways

Following the operation the visual acuity is very seldom disturbed even in the very few cases in the present material in which there was a suspicion of macular splitting This is probably due to the fact that the homonymous fibres from the macula in the temporal lobe are localized medially in the optic radiation and thus close to important cerebral areas which the neuro surgeon attempts to spare during the operation for example the posterior parts of the superior temporal gyrus

The importance of the extent of the lobectomy has also been demonstrated in the present material where the number of visual field defects including the lower quadrants is significantly higher in the right sided lobectomies than in the left sided (Table II) 2 and 11 per cent respectively which corresponds well with the fact that right sided lobectomies are generally larger than left sided Apart from this finding we like Falconer & Wilson (1958) have not found any significant correlations between the extent of the lobectomy and the degree of the anopia As mentioned previously 33 % of the patients had retained their normal visual fields following resections varying in extent from 5 5 to 7 cm Also in accordance with these authors we observed that an opening of the tip of the lateral ventricle did not necessarily result in a postoperative visual field defect The individual variations in the course of Meyer s loop as suggested by Ronne (1915) can explain this observation

Conclusion

With regard to the architecture of the visual pathways in the temporal lobe the present investigation is in full agreement with surveys previously published Primarily the purpose was not to attempt to supply new information about the anatomy of the visual pathways but rather based on clinical observations to correlate the importance of anterior temporal lobectomy in the treatment of drug resistant temporal lobe epilepsy with the ophthalmological complica tions which might result from this operation and above all to the homonymous visual field defects

This topic is a typical borderline subject between the two related specia lities neurology and ophthalmology From the neurological point of view a unilateral temporal lobectomy has proved to be successful in relieving pa tients with drug resistant temporal lobe epilepsy of their seizures and has in many cases also made a social rehabilitation possible From the ophthalmolo

gical point of view a visual field defect was found to be a postoperative com plication in two thirds of the patients but in the majority of these cases it was of only minor importance (viz the visual field defects affecting the upper quadrants only)

Based on the knowledge accumulated in literature during the last 60 to 70 years and on our own experience it must be emphasized that very marked individual variations are observed in the course of the visual pathways in the temporal lobe especially regarding the Meyer s loop even though there is correlation between the extent of the temporal lobe resection and the post operative presence of a visual field defect Accordingly it is not possible to predict whether a visual field defect will occur or not not can the extent of any postoperative defect be predicted

If the relatively few cases (13 of 74) with visual field defects including the lower quadrants are set against the satisfactory results regarding relief from seizures and social rehabilition most importance must be attached to these results provided that the visual acuity remains unaffected

The present investigation also supports the opinion that this operation should preferably be carried out in childhood adolescence or early adulthood and should definitely be undertaken as soon as the epilepsy has proved to be re sistant to medication

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Frank W Law The History and Traditions of the Moorfields Eye Hospital Vol II London 1975 H K Lewis & Co 299 pages 70 illustrations Price £ 4

The world famous Moorfields Eye Hospital or Moorfields in London was opened on 25th March 1805 The first one hundred years of its history were described by Edward Treacher Collins in 1929 Frank W Law has now supplemented this and brought the history up to date in a book covering the subsequent 70 years With his 47 years of service in the social and professional life of Moorfields Law has first hand experience of a considerable part of this period

The book provides a detailed description of the successive building extensions and modernisations which have taken place and gives insight into the many financial administrative and sociological problems of this period Most important of all is the account given of the professional activity of the hospital which in many a case is regarded as a pioneer achievement and reflects the development of Ophthalmology In addition the book contains a series of biographies of well known colleages and their various achievements

In Scandinavia an eye ward is usually of modest size and integrated into a larger hospital with various specialities To the reviewer Moorfields represents a vast institution whose function it would appear difficult to administrate In Law s book one is able to recognise the outstanding practical pedagogic and scientific achievements which are the symbol of co operation and adaptation to the needs of the time One has to admire Law for this considerable work and for his knowledgeable and well balanced presentation which surely comes not only from duty and devotion but also from genuine love

The book even though it is primarily directed to those with a personal connection to Moorfields makes useful and good reading

P Brændstrup

E Bessiere Aspects cliniques des modifications de la tension oculaire Mason & Cie Paris 1975 Pages 232 45 figures Price 145 F

In addition to the above mentioned monograph which is concerned with clinical aspects the author has in the same series published a monograph entitled Aspects physiopathologiques des modifications de la tension oculaire

In the monograph in question a traditional clinical account of the primary and secondary glaucomas is given The description of the different ways in which secondary glaucoma can manifest itself covers almost half of the book A short description of ocular hypotension completes the monograph Each chapter ends with a summary in English together with a literature list which however contains only a few references subsequent to 1971

The monograph does not essentially contribute anything new when compared with the other concise and systematic descriptions of the different clinical manifestations of glaucoma

K Nørskov

J T Pearlman Ed Xth I S C E R G Symposium Los Angeles 1972 Documenta Ophthalmologica Proceedings Series vol II Junk Haag 1973 292 pages 222 illustrations Price Dutch Glds 75

This volume contains papers from the Xth symposium of the International Society for Clinical Electroretinography held in Los Angeles in 1972 The articles concern ERG EOG and VER (visual evoked (cortical) response) The main topics are ERG in systemic disease retinal vascular disease and light induced retinal changes Apart from pure clinical studies the book comprises articles of experimental and theoretical nature

Many and considerable advances in the field of clinical electroretinography have been made since ISCERG s first symposium meeting in Stockholm in 1960 (Acta Ophthal suppl 70 1962) Furthermore, other electrophysiological examination techniques such as EOG and VER have proved themselves to be clinically useful It was therefore suggested that the name of the Society be changed to International Society for Clinical Electro Physiology of the Visual System

Together with the accounts of the previous symposia the book can be recommended to all those who wish to keep abreast of the advances made in these particular fields of research *Sv E Simonsen*

Rudolf Sachsenweger (ed) Neuroophthalmologie V E B Georg Thieme Leipzig 1975 677 pages 332 illustrations 32 tab 130–M

This book is written in German by the professor at the eye clinic at the Karl Marx University in Leipzig East Germany and by his colleagues from the neurologic neuro surgery dermatologic anatomic physiologic otorhinologic and other departments from the university 36 authors in all

The result is a precise didactic short book concerning all the neuroophthalmic problems covering the anatomic aspects examination methods (without mentioning EMI scanning sphycmography and corneal nylon aestesiometry) Sections concerning ophthalmoscopy perimetry motility pupil with pharmacological tests orbita Topic diagnostics are very well illustrated with diagrams of the anatomic lesion in the region concerned and a corresponding figure of the patient with paretic and anaestec regions outmapped

Special chapters deals with multiple sclerosis supratentoriel and infratentoriel cranial tumours inflammation in the central nervesystem (with 15 pages of tables) *head ache* epilepsia hemicrania congenital diseases toxicology etc

The nasal fundus ectasia is only mentioned (cf Dag Riise Acta ophthal (Kbh) suppl 126)

The diagrams concerning perimetry (p 58) and ocular palsies in the primary and secundary positions and head positions are very illustrative

There are none or only very few references to the literature The English word is often given after the German terminology (cover test cerebellar fits etc)

The therapy differs only in a few cases from the usual practice The biopsy at arteritis temporalis is claimed to be of therapeutic effect. I would only rely on steroids!

This book is recommended to the ophthalmologist as a didatic well illustrated textbook.

It is further recommended to the ophthalmic practioner as a repetition course and a very well equiped book for short advice. *M S Norn*

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